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I, LEANNE MYNOTT, MANAGER EXAMINATION SUPPORT AND SALES hereby certify that annexed is a true copy of the Provisional specification in connection with Application No. 2003906686 for a patent by CYTOPIA PTY LTD OF BAKER MEDICAL RESEARCH INSTITUTE as filed on 03 December 2003.

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Twenty-first day of December 2004

A handwritten signature in black ink.

LEANNE MYNOTT
MANAGER EXAMINATION SUPPORT
AND SALES



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AUSTRALIA
Patents Act 1990 (Cth)

PROVISIONAL SPECIFICATION

Cytopia Pty Ltd

Invention Title

Azole-based kinase inhibitors

The invention is described in the following statement:

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AZOLE-BASED KINASE INHIBITORS**FIELD OF THE INVENTION**

The present invention relates to the field of inhibitors of protein tyrosine kinases.

BACKGROUND OF THE INVENTION

5 Protein kinases are a family of enzymes that catalyse the phosphorylation of specific residues in proteins. In general protein kinases fall into several groups; those which preferentially phosphorylate serine and/or threonine residues, those which preferentially phosphorylate tyrosine residues and those which phosphorylate both tyrosine and Ser/Thr residues. Protein kinases are therefore key elements in signal transduction
10 pathways responsible for transducing extracellular signals, including the action of cytokines on their receptors, to the nuclei, triggering various biological events. The many roles of protein kinases in normal cell physiology include cell cycle control and cell growth, differentiation, apoptosis, cell mobility and mitogenesis.

Protein kinases include, for example, but are not limited to, members of the Protein
15 Tyrosine Kinase family (PTKs), which in turn can be divided into the cytoplasmic PTKs and the receptor PTKs (RTKs). The cytoplasmic PTKs include the SRC family, (including: BLK; FGR; FYN; HCK; LCK; LYN; SRC; YES and YRK); the BRK Family (including: BRK; FRK, SAD; and SRM); the CSK family (including: CSK and CTK); the BTK family, (including BTK; ITK; TEC; MKK2 and TXK), the Janus kinase family, (including: JAK1,
20 JAK2, JAK3 and Tyk2), the FAK family (including, FAK and PYK2); the Fes family (including FES and FER), the ZAP70 family (including ZAP70 and SYK); the ACK family (including ACK1 and ACK2); and the Abl family (including ABL and ARG). The RTK family includes the EGF-Receptor family (including, EGFR, HER2, HER3 and HER4); the Insulin Receptor family (including, INS-R and IGF1-R); the PDGF-Receptor family
25 (including PDGFR α , PDGFR β , CSF1R, KIT, FLK2); the VEGF-Receptor family (including: FLT1, FLK1 and FLT4); the PGF-Receptor family (including: FGFR1, FGFR2, FGFR3 and FGFR4); the CCK4 family (including CCK4); the MET family (including MET and RON); the TRK family (including TRKA, TRKB, and TRKC); the AXL family (including AXL, MER, and SKY); the TIE/TEK family (including TIE and TIE2/TEK); the
30 EPH family (including EPHA1, EPHA2, EPHA3, EPHA4, EPHA5, EPHA6, EPHA7, EPHA8, EPHB1, EPHB2, EPHB3, EPHB4, EPHB5, EPHB6); the RYK family (including

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RYK); the MCK family (including MCK and TYRO10); the ROS family (including ROS); the RET family (including RET); the LTK family (including LTK and ALK); the ROR family (including ROR1 and ROR2); The Musk family (including Musk); the LMR family including LMR1, LMR2 and LMR3); and the SuRTK106 family (including SuRTK106).

5 Similarly, the serine /threonine specific kinases comprise a number of distinct sub-families, including; the extracellular signal regulated kinases, (p42/ERK2 and p44/ERK1); c-Jun NH2-terminal kinase (JNK); cAMP-responsive element-binding protein kinases (CREBK); cAMP-dependent kinase (CAPK); mitogen-activated protein kinase-activated protein kinase (MAPK and its relatives); stress-activated protein kinase p38/SAPK2; mitogen-and stress-activated kinase (MSK); protein kinases, PKA, PKB and PKC *inter alia*.

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Additionally, the genomes of a number of pathogenic organisms possess genes encoding protein kinases. For example, the malarial parasite *Plasmodium falciparum* and viruses such as HPV and Hepatitis viruses appear to bear kinase related genes.

15 Inappropriately high protein kinase activity has been implicated in many diseases resulting from abnormal cellular function. This might arise either directly or indirectly, for example by failure of the proper control mechanisms for the kinase, related for example to mutation, over-expression or inappropriate activation of the enzyme; or by over- or under-production of cytokines or growth factors also participating in the

20 transduction of signals upstream or downstream of the kinase. In all of these instances, selective inhibition of the action of the kinase might be expected to have a beneficial effect. Diseases where aberrant kinase activity has been implicated include: diabetes; restenosis; atherosclerosis; fibrosis of the liver and kidney; ocular diseases; myelo- and lymphoproliferative disorders; cancer such as prostate cancer, colon cancer, breast cancer,

25 head and neck cancer, leukemia and lymphoma; and, auto-immune diseases such as Atopic Dermatitis, Asthma, rheumatoid arthritis, Crohn's disease, psoriasis, Crouzon syndrome, achondroplasia, and thanatophoric dysplasia.

The JAK family of protein tyrosine kinases (PTKs) play a central role in the cytokine dependent regulation of the proliferation and end function of several important cell types of the immune system.

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A direct comparison of the four currently known mammalian JAK family members reveals the presence of seven highly conserved domains (Harpur *et al*, 1992). In seeking a nomenclature for the highly conserved domains characteristic of this family of PTKs, the classification used was guided by the approach of Pawson and co-workers (Sadowski *et al*, 1986) in their treatment of the SRC homology (SH) domains. The domains have been 5 enumerated accordingly with most C-terminal homology domain designated JAK Homology domain 1 (JH1). The next domain N-terminal to JH1 is the kinase-related domain, designated here as the JH2 domain. Each domain is then enumerated up to the JH7 located at the N-terminus. The high degree of conservation of these JAK homology (JH) domains suggests that they are each likely to play an important role in the cellular 10 processes in which these proteins operate. However, the boundaries of the JAK homology domains are arbitrary, and may or may not define functional domains. Nonetheless, their delineation is a useful device to aid the consideration of the overall 15 structural similarity of this class of proteins.

15 The feature most characteristic of the JAK family of PTKs is the possession of two kinase-related domains (JH1 and JH2) (Wilks *et al*, 1991). The putative PTK domain of JAK1 (JH1) contains highly conserved motifs typical of PTK domains, including the presence of a tyrosine residue at position 1022 located 11 residues C-terminal to 20 sub-domain VII that is considered diagnostic of membership of the tyrosine-specific class of protein kinases. Alignment of the human JAK1 PTK domain (255 amino acids), with other members of the PTK class of proteins revealed homology with other functional PTKs (for example, 28% identity with c-fes (Wilks and Kurban, 1988) and 37% homology to TRK (Kozma *et al*, 1988). The JH1 domains of each of the JAK family members possess 25 an interesting idiosyncrasy within the highly conserved sub-domain VIII motif (residues 1015 to 1027 in JAK2) that is believed to lie close to the active site, and define substrate specificity. The phenylalanine and tyrosine residues flanking the conserved tryptophan in this motif are unique to the JAK family of PTKs. Aside from this element, the JH1 domains of each of the members of the JAK family are typical PTK domains.

30 The central role played by the JAK family of protein tyrosine kinases in the cytokine dependent regulation of the proliferation and end function of several important cell types means that agents which inhibit JAK are useful in the prevention and chemotherapy of disease states dependent on these enzymes. Potent and specific inhibitors of each of the

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currently known four JAK family members will provide a means of inhibiting the action of those cytokines that drive immune pathologies, such as asthma (e.g. IL-13; JAK1, JAK2), and leukemia/lymphoma (e.g. IL-2: JAK1 and JAK3).

Furthermore, certain types of cancer such as prostate cancer develop autocrine production of certain cytokines as a selectable mechanism of developing growth and / or metastatic potential. An example of this is cancer of the prostate, where IL-6 is produced by and stimulates the growth of prostate cancer cell lines such as TSU and 'TC3 (Spiotto MT, and Chung TD, 2000). Interestingly, levels of IL-6 are elevated in sera of patients with metastatic prostate cancer.

10 A great deal of literature covers the area of cytokine signalling. The present inventors have focussed on the JAK/STAT pathway that is involved in the direct connection of cytokine receptor to target genes (such as cell cycle regulators (e.g. p21) and anti-apoptosis genes (such as Bcl-X_l)).

The JAK/STAT Pathway

15 The delineation of a particularly elegant signal transduction pathway downstream of the non-protein tyrosine kinase cytokine receptors has recently been achieved. In this pathway the key components are: (i) A cytokine receptor chain (or chains) such as the Interleukin-4 receptor or the Interferon γ receptor; (ii) a member (or members) of the JAK family of PIKs; (iii) a member(s) of the STAT family of transcription factors, and (iv) a sequence specific DNA element to which the activated STAT will bind.

20 A review of the JAK/STAT literature offers strong support to the notion that this pathway is important for the recruitment and marshalling of the host immune response to environmental insults, such as viral and bacterial infection. This is well exemplified in Table 1 and Table 2. Information accumulated from gene knock-out experiments have underlined the importance of members of the JAK family to the intracellular signalling triggered by a number of important immune regulatory cytokines. The therapeutic possibilities stemming from inhibiting (or enhancing) the JAK/STAT pathway are thus largely in the sphere of immune modulation, and as such are likely to be promising drugs for the treatment of a range of pathologies in this area. In addition to the diseases listed in Tables 1 and 2, inhibitors of JAKs could be used as immunosuppressive agents for organ

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transplants and autoimmune diseases such as lupus, multiple sclerosis, rheumatoid arthritis, Type I diabetes, autoimmune thyroid disorders, Alzheimer's disease and other autoimmune diseases. Additionally, treatment of cancers such as prostate cancer by JAK inhibitors is indicated.

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Table 1

Disease Type	Cell Types Involved	Characteristics
Atopy Allergic Asthma Atopic Dermatitis (Eczema) Allergic Rhinitis	(Mast Cells (Eosinophils (T-Cells (B-Cells	T-cell activation of B-cells followed by IgE mediated activation of resident Mast cells and Eosinophils
Cell Mediated Hypersensitivity Allergic Contact Dermatitis Hypersensitivity Pneumonitis	(T-cells (B-cells	T-cell hypersensitivity
Rheumatic Diseases Systemic Lupus Erythematosus (SLE) Rheumatoid Arthritis Juvenile Arthritis Sjögren's Syndrome Scleroderma Polymyositis Ankylosing Spondylitis Psoriatic Arthritis	(Monocytes (Macrophages (Neutrophils (Mast Cells (Eosinophils (T-Cells (B-Cells	Cytokine Production (e.g. TNF, IL-1, CSF-1, GM-CSF) T-cell Activation JAK/STAT activation
Viral Diseases Epstein Barr Virus (EBV) Hepatitis B Hepatitis C HIV HTLV 1 Varicella-Zoster Virus (VZV) Human Papilloma Virus (HPV)	Lymphocytes Hepatocytes Hepatocytes Lymphocytes Lymphocytes Fibroblasts Epithelial cells	JAK/STAT Activation JAK/STAT Activation JAK/STAT Inhibition JAK/STAT Activation JAK/STAT Activation JAK/STAT Inhibition JAK/STAT Inhibition
Cancer Leukemia Lymphoma	Leucocytes Lymphocytes	(Cytokine production (JAK/STAT Activation

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Target Disease	Cytokine	JAK family member	Strength of Association
Asthma	IL-4 & IL-9	JAK1 & JAK3	+++
	IL-13	JAK1 & JAK2	+++
	IL-5	JAK2	+++
Eczema	IL-4	JAK1 & JAK3	+++
	IFN- α	JAK1 & JAK2	+++
Food Allergy	IL-4	JAK1 & JAK3	+++
Inflammatory Bowel Disease & Crohn's Disease	IL-4	JAK1 & JAK3	+++
Leukaemia And Lymphoma	(IL-2)	JAK3, JAK1 & JAK2	+++
Cutaneous Inflammation	GM-CSF & IL-6	JAK1 & JAK2	+++
Immune Suppression By Solid Tumour	IL-10	JAK1 & TYK2	+++
Prostate Cancer	IL-6	JAK1, JAK2 & Tyk2	+++

Table 2: Diseases Potentially Treatable By JAK-Based Drug Therapies

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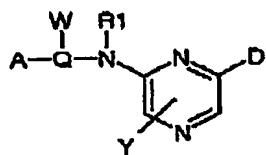
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SUMMARY OF THE INVENTION

The present inventors have found that a group of compounds based upon the disubstituted pyrazine scaffold I, are inhibitors of tyrosine kinases.

Accordingly, in a first aspect the present invention consists in a compound of the general

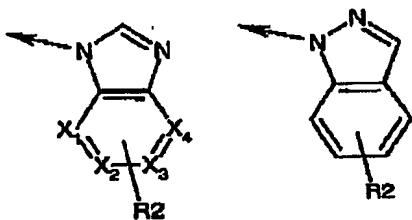
5 formula



I

or pharmaceutically acceptable prodrugs, salts, hydrates, solvates, crystal forms or diastereomers thereof, wherein:

10 D is a heterocyclic ring selected from:



where X₁, X₂, X₃, X₄ are optionally substituted carbon, or one of X₁, X₂, X₃, X₄ is nitrogen and the rest are optionally substituted carbon;

15 R2 is 0-3 substituents independently chosen from H, halogen, C₁₋₄alkyl, CF₃, OCF₃, OCHE₂, CN, aryl, hetaryl, C₁₋₄alkylOH, C₁₋₄alkylNR3R4, C₁₋₄alkylhetaryl, OC₁₋₄alkyl, OC₁₋₄alkylNR3R4, OC₁₋₄alkylhetaryl, OC₁₋₄alkylOH, CO₂R3, CONR3R4, NR3R4, nitro, NR3COR4, NR5CONR3R4, NR3SO₂R4, C₁₋₄alkylNR3COR4, C₁₋₄alkylNR5CONR3R4, C₁₋₄alkylNR3SO₂R4;

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R3, R4 are each independently H, C₁₋₄alkyl, C₁₋₄alkylOH, C₁₋₄alkylNR19R20, C₁₋₄alkyl cycloalkyl, C₁₋₄ cyclohetalkyl, aryl, C₁₋₄ alkylaryl, hetaryl, C₁₋₄ alkylhetaryl, or may be joined to form an optionally substituted 3-8 membered (saturated or unsaturated) ring optionally containing an atom selected from O, S, NR6;

5

and R5 is selected from H, C₁₋₄alkyl, aryl or hetaryl;

R6 is selected from H, C₁₋₄alkyl, C₁₋₄alkylNR19R20, aryl, hetaryl, C₁₋₄ alkyl aryl, C₁₋₄alkyl hetaryl;

R19, R20 are each independently selected from H, C₁₋₄alkyl;

10 R1 is H, C₁₋₄alkyl, C₁₋₄cycloalkyl, or may form a 5-8 membered ring onto the ortho position of ring A;

Q is a bond, CH₂, C₁₋₄alkyl;

A is aryl, hetaryl optionally substituted with 0-3 substituents independently chosen from halogen, C₁₋₄alkyl, CF₃, OCF₃, CN, NR8R9, aryl, hetaryl, C₁₋₄aryl, C₁₋₄hetaryl, C₁₋₄alkylNR8R9, OC₁₋₄alkylNR8R9, nitro, NR10C₁₋₄NR8R9, NR8COR9, NR10CONR8R9, NR8SO₂R9, CONR8R9, CO₂R8;

R8 and R9 are each independently H, C₁₋₄alkyl, aryl or together form an optionally substituted 4-8 membered ring which may contain a heteroatom selected from O, S, NR11;

20

R10 is selected from H, C₁₋₄alkyl;

R11 is selected from H, C₁₋₄alkyl;

W is selected from H, C₁₋₄alkyl, C₂₋₄alkenyl or may form a 5-8 membered ring onto the ortho position of ring A; where C₁₋₄alkyl or C₂₋₄alkenyl may be optionally substituted with C₁₋₄alkyl, OH, OC₁₋₄alkyl, NR12R13;

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R12, and R13 are each independently H, C₁₋₄alkyl, or may be joined to form an optionally substituted 3-8 membered ring optionally containing an atom selected from O, S, NR14;

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R14 is selected from H, C₁₋₄ alkyl;Y is 0-2 substituents selected from H, C₁₋₄ alkyl, NR15R16;R15 and R16 are independently selected from H, C₁₋₄ alkyl.

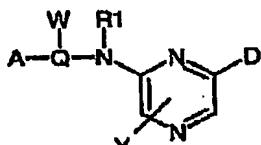
In a second aspect the present invention consists in a composition comprising a carrier
5 and at least one compound of the first aspect of the invention.

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In a third aspect the present invention consists in a method of treating a tyrosine kinase-associated disease state, the method comprising administering a therapeutically effective amount of at least one compound of the first aspect of the invention or a therapeutically effective amount of a composition of the second aspect of the invention.

10 DETAILED DESCRIPTION OF THE INVENTION

The present inventors have found that a group of compounds based upon the disubstituted pyrazine scaffold I, are inhibitors of tyrosine kinases.

Accordingly, in a first aspect the present invention consists in a compound of the general formula



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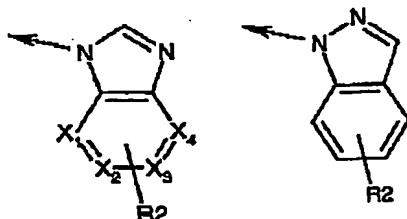
or pharmaceutically acceptable prodrugs, salts, hydrates, solvates, crystal forms or diastereomers thereof, wherein:

D is a heterocyclic ring selected from

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where X_1, X_2, X_3, X_4 are optionally substituted carbon, or one of X_1, X_2, X_3, X_4 is nitrogen and the rest optionally substituted carbon;

5 R2 is 0-3 substituents independently chosen from H, halogen, C_{1-4} alkyl, CF_3 , OCF_3 , $OCHF_2$, CN, aryl, hetaryl, C_{1-4} alkylOH, C_{1-4} alkylNR3R4, C_{1-4} alkylhetaryl, OC_{1-4} alkyl, OC_{1-4} alkylNR3R4, OC_{1-4} alkylhetaryl, OC_{1-4} alkylOH, CO_2R_3 , $CONR3R4$, NR3R4, nitro, NR3COR4, NR5CONR3R4, NR3SO₂R4, C_{1-4} alkylNR3COR4, C_{1-4} alkylNR5CONR3R4, C_{1-4} alkylNR3SO₂R4;

10 R3, R4 are each independently H, C_{1-4} alkyl, C_{1-4} alkylOH, C_{1-4} alkylNR19R20, C_{1-4} alkyl cycloalkyl, C_{1-4} cyclohetalkyl, aryl, C_{1-4} alkylaryl, hetaryl, C_{1-4} alkylhetaryl, or may be joined to form an optionally substituted 3-8 membered (saturated or unsaturated) ring optionally containing an atom selected from O, S, NR6;

and R5 is selected from H, C_{1-4} alkyl, aryl or hetaryl;

15 R6 is selected from H, C_{1-4} alkyl, C_{1-4} alkylNR19R20, aryl, hetaryl, C_{1-4} alkyl aryl, C_{1-4} alkyl hetaryl;

R19, R20 are each independently selected from H, C_{1-4} alkyl;

R1 is H, C_{1-4} alkyl, C_{1-4} cycloalkyl, or may form a 5-8 membered ring onto the ortho position of ring A;

20 Q is a bond, CH_2 , C_{1-4} alkyl;

A is aryl, hetaryl optionally substituted with 0-3 substituents independently chosen from halogen, C_{1-4} alkyl, CF_3 , OCF_3 , CN, NR8R9, aryl, hetaryl, C_{1-4} aryl,

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C_{1-4} hetaryl, C_{1-4} alkylNR8R9, OC_{1-4} alkylNR8R9, nitro, NR10 C_{1-4} NR8R9, NR8COR9,
NR10CONR8R9, NR8SO₂R9, CONR8R9, CO₂R8;

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R8 and R9 are each independently H, C_{1-4} alkyl, aryl or together form an
optionally substituted 4-8 membered ring which may contain a heteroatom
selected from O, S, NR11;

R10 is selected from H, C_{1-4} alkyl;

R11 is selected from H, C_{1-4} alkyl;

10

W is selected from H, C_{1-4} alkyl, C_{2-6} alkenyl or may form a 5-8 membered ring onto
the ortho position of ring A; where C_{1-4} alkyl or C_{2-6} alkenyl may be optionally
substituted with C_{1-4} alkyl, OH, OC_{1-4} alkyl, NR12R13;

R12, and R13 are each independently H, C_{1-4} alkyl, or may be joined to form
an optionally substituted 3-8 membered ring optionally containing an atom
selected from O, S, NR14;

R14 is selected from H, C_{1-4} alkyl;

15

Y is 0-2 substituents selected from H, C_{1-4} alkyl, NR15R16;

R15 and R16 are independently selected from H, C_{1-4} alkyl.

In the above description it will be appreciated that:

C_{1-4} alkyl means an unsubstituted or optionally substituted straight or branched
alkyl chain

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Aryl means unsubstituted or optionally substituted phenyl or naphthyl.

Hetaryl means a unsubstituted or optionally substituted 5- or 6-membered
heteroaromatic ring containing one or more heteroatoms selected from O, N, S.

Cycloalkyl means a 3-8 membered saturated ring

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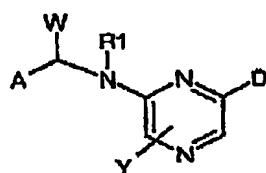
Cyclohetalkyl means a 3-8 membered saturated ring containing 1-3 heteroatoms
selected from O, S, NR17,

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where R17 is H, C₁₋₄ alkyl, aryl, hetaryl.

In a further preferred embodiment the compound is selected from compounds of the general formula II.

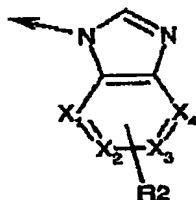


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or pharmaceutically acceptable prodrugs, salts, hydrates, solvates, crystal forms or diastereomers thereof, wherein:

D is a heterocyclic ring selected from:



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where X₁, X₂, X₃, X₄ are optionally substituted carbon, or one of X₁, X₂, X₃, X₄ is N and the rest optionally substituted carbon;

15

R2 is 0-3 substituents independently chosen from H, halogen, C₁₋₄ alkyl, CF₃, OCF₃, OCHF₂, CN, aryl, hetaryl, C₁₋₄ alkylOH, C₁₋₄ alkylNR3R4, C₁₋₄ alkylhetaryl, OC₁₋₄ alkyl, OC₁₋₄ alkylNR3R4, OC₁₋₄ alkylhetaryl, OC₁₋₄ alkylOH, CO₂R3, CONR3R4, NR3R4, nitro, NR3COR4, NR5CONR3R4, NR3SO₂R4, C₁₋₄ alkylNR3COR4, C₁₋₄ alkylNR5CONR3R4, C₁₋₄ alkylNR3SO₂R4;

R3, R4 are each independently H, C₁₋₄ alkyl, C₁₋₄ alkylOH, C₁₋₄ alkylNR19R20, C₁₋₄ alkyl cycloalkyl, C₁₋₄ cyclohetalkyl, aryl, C₁₋₄ alkylaryl, hetaryl, C₁₋₄ alkylhetaryl, or may be joined to form an optionally substituted 3-8

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membered (saturated or unsaturated) ring optionally containing an atom selected from O, S, NR6;

and R5 is selected from H, C₁₋₄ alkyl, aryl or hetaryl;

5

R6 is selected from H, C₁₋₄ alkyl, C₁₋₄alkylNR19R20, aryl, hetaryl, C₁₋₄ alkyl aryl, C₁₋₄alkyl hetaryl;

R19, R20 are each independently selected from H, C₁₋₄alkyl;

R1 is H, C₁₋₄ alkyl, C₁₋₆ cycloalkyl, or may form a 5-8 membered ring onto the ortho position of ring A;

10

A is aryl, hetaryl optionally substituted with 0-3 substituents independently chosen from halogen, C₁₋₄alkyl, CF₃, OCF₃, CN, NR8R9, aryl, hetaryl, C₁₋₄aryl, C₁₋₄hetaryl, C₁₋₄ alkylNR8R9, OC₁₋₄ alkylNR8R9, nitro, NR10C₁₋₄NR8R9, NR8COR9, NR10CONR8R9, NR8SO₂R9, CONR8R9, CO₂R8;

15

R8 and R9 are each independently H, C₁₋₄ alkyl, aryl or together form an optionally substituted 4-8 membered ring which may contain a heteroatom selected from O, S, NR11;

R10 is selected from H, C₁₋₄ alkyl;

R11 is selected from H, C₁₋₄ alkyl;

20

W is selected from H, C₁₋₄alkyl, C₂₋₆alkenyl or may form a 5-8 membered ring onto the ortho position of ring A; where C₁₋₄alkyl or C₂₋₆alkenyl may be optionally substituted with C₁₋₄alkyl, OH, OC₁₋₄alkyl, NR12R13;

R12, and R13 are each independently H, C₁₋₄alkyl, or may be joined to form an optionally substituted 3-8 membered ring optionally containing an atom selected from O, S, NR14;

R14 is selected from H, C₁₋₄ alkyl;

25

Y is 0-2 substituents selected from H, C₁₋₄ alkyl, NR15R16;

R15 and R16 are independently selected from H, C₁₋₄alkyl.

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In the above description it will be appreciated that:

C_{1-4} alkyl means an unsubstituted or optionally substituted straight or branched alkyl chain

Aryl means unsubstituted or optionally substituted phenyl or naphthyl.

5 Hetaryl means a unsubstituted or optionally substituted 5- or 6-membered heteroaromatic ring containing one or more heteroatoms selected from O, N, S.

Cycloalkyl means a 3-8 membered saturated ring

Cyclohetalkyl means a 3-8 membered saturated ring containing 1-3 heteroatoms selected from O, S, NR17,

10 where R17 is H, C_{1-4} alkyl, aryl, hetaryl.

The compounds of this invention include all conformational isomers (eg, cis and trans isomers). The compounds of the present invention have asymmetric centers and therefore exist in different enantiomeric and diastereomeric forms. This invention relates to the use of all optical isomers and stereoisomers of the compounds of the present invention, and mixtures thereof, and to all pharmaceutical compositions and methods of treatment that may employ or contain them. In this regard, the invention includes both the E and Z configurations. The compounds of formula I may also exist as tautomers. This invention relates to the use of all such tautomers and mixtures thereof.

20 This invention also encompasses pharmaceutical compositions containing prodrugs of compounds of the formula I. This invention also encompasses methods of treating or preventing disorders that can be treated or prevented by the inhibition of protein kinases, such as JAK comprising administering prodrugs of compounds of the formula I. Compounds of formula I having free amino, amido, hydroxy or carboxylic groups can be converted into prodrugs. Prodrugs include compounds wherein an amino acid residue, 25 or a polypeptide chain of two or more (eg, two, three or four) amino acid residues which are covalently joined through peptide bonds to free amino, hydroxy and carboxylic acid groups of compounds of formula I. The amino acid residues include the 20 naturally occurring amino acids commonly designated by three letter symbols and also include, 4-hydroxyproline, hydroxylysine, demosine, isodemosine, 3-methylhistidine, norvalin, beta-

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alanine, gamma-aminobutyric acid, citrulline, homocysteine, homoserine, ornithine and methioine sulfone. Prodrugs also include compounds wherein carbonates, carbamates, amides and alkyl esters which are covalently bonded to the above substituents of formula I through the carbonyl carbon prodrug sidechain. Prodrugs also include phosphate derivatives of compounds of formula I (such as acids, salts of acids, or esters) joined through a phosphorus-oxygen bond to a free hydroxyl of compounds of formula I.

5 In a still further preferred embodiment the compound possesses *S* chirality at the chiral carbon bearing W, where W is C₁₋₄ alkyl. The compound can be used as a purified isomer or as a mixture of any ratio of isomers. It is however preferred that the mixture comprises 10 at least 70%, 80%, 90%, 95%, or 99% of the preferred isomer.

In a second aspect the present invention consists in a composition comprising a carrier and at least one compound of the first aspect of the invention.

15 In a third aspect the present invention consists in a method of treating a tyrosine kinase-associated disease state, the method comprising administering a therapeutically effective amount of at least one compound of the first aspect of the invention or a therapeutically effective amount of a composition of the second aspect of the invention.

In a further preferred embodiment the disease state involves JAK1, JAK2, JAK3 or TYK2.

20 In a preferred embodiment of the present invention the disease state is selected from the group consisting of Atopy, such as Allergic Asthma, Atopic Dermatitis (Eczema), and Allergic Rhinitis; Cell Mediated Hypersensitivity, such as Allergic Contact Dermatitis and Hypersensitivity Pneumonitis; Rheumatic Diseases, such as Systemic Lupus Erythematosus (SLE), Rheumatoid Arthritis, Juvenile Arthritis, Sjögren's Syndrome, Scleroderma, Polymyositis, Ankylosing Spondylitis, Psoriatic Arthritis; Other autoimmune diseases such as Type I diabetes, autoimmune thyroid disorders, and 25 Alzheimer's disease; Viral Diseases, such as Epstein Barr Virus (EBV), Hepatitis B, Hepatitis C, HIV, HTLV 1, Varicella-Zoster Virus (VZV), Human Papilloma Virus (HPV), Cancer, such as Leukemia, Lymphoma and Prostate Cancer.

30 As used herein the term "tyrosine kinase-associated disease state" refers to those disorders which result from aberrant tyrosine kinase activity, in particular JAK activity and/or which are alleviated by inhibition of one or more of these enzymes.

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In further aspects the present invention provides the use of the compounds described in the preparation of medicaments for the treatment of JAK-associated disease states.

As used herein the term "JAK", "JAK kinase" or "JAK family" refers to protein tyrosine kinases which possess the characterizing features of JAK1, JAK2, JAK3 and TYK as

5 described herein.

The present invention provides pharmaceutical compositions comprising at least one of the compounds of the present invention capable of treating a JAK-associated disorder in an amount effective therefor, and a pharmaceutically acceptable vehicle or diluent. The compositions of the present invention may contain other therapeutic agents as described 10 below, and may be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

15 The compounds of the present invention may be administered by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; buccally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intracisternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally such as by inhalation spray; topically, 20 such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The compounds may, for example, be administered in a form suitable for immediate release or extended release. Immediate release or extended release may be achieved by the use of suitable pharmaceutical compositions comprising the present 25 compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The compounds may also be administered liposomally.

In addition to primates, such as humans, a variety of other mammals can be treated according to the method of the present invention. For instance, mammals including, but 30 not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine,

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ovine, equine, canine, feline, rodent or murine species can be treated. However, the method can also be practiced in other species, such as avian species (e.g., chickens).

Diseases and conditions associated with inflammation and infection can be treated using the method of the present invention. In a preferred embodiment, the disease or condition 5 is one in which the actions of eosinophils and/or lymphocytes are to be inhibited or promoted, in order to modulate the inflammatory response.

The subjects treated in the above methods, in whom which JAK inhibition is desired, are mammals, including, but not limited to, cows, sheep, goats, horses, dogs, cats, guinea pigs, rats or other bovine, ovine, equine, canine, feline, rodent or murine species, and 10 preferably a human being, male or female.

The term "therapeutically effective amount" means the amount of the subject composition that will elicit the biological or medical response of a tissue, system, animal or human that is being sought by the researcher, veterinarian, medical doctor or other clinician.

The term "composition" as used herein is intended to encompass a product comprising 15 the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts. By "pharmaceutically acceptable" it is meant the carrier, diluent or excipient must be compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

20 The terms "administration of" and/or "administering a" compound should be understood to mean providing a compound of the invention to the individual in need of treatment.

The pharmaceutical compositions for the administration of the compounds of this invention may conveniently be presented in dosage unit form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of 25 bringing the active ingredient into association with the carrier which constitutes one or more accessory ingredients. In general, the pharmaceutical compositions are prepared by uniformly and intimately bringing the active ingredient into association with a liquid carrier or a finely divided solid carrier or both, and then, if necessary, shaping the product into the desired formulation. In the pharmaceutical composition the active object 30 compound is included in an amount sufficient to produce the desired effect upon the

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process or condition of diseases. As used herein, the term "composition" is intended to encompass a product comprising the specified ingredients in the specified amounts, as well as any product which results, directly or indirectly, from combination of the specified ingredients in the specified amounts.

5 The pharmaceutical compositions containing the active ingredient may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, hard or soft capsules, or syrups or elixirs. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such

10 compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the

15 gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated to form osmotic therapeutic tablets for control release.

20 Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

25 Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxy-propylmethylcellulose, sodium alginate, polyvinyl-pyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide,

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for example lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethylneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylne sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl, p-hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally- occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

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Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions may be in the form of a sterile injectable aqueous or

5 oleagenous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1,3-butane diol. Among the acceptable vehicles and solvents that

10 may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

15 The compounds of the present invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials are cocoa butter and polyethylene glycols.

20 For topical use, creams, ointments, jellies, solutions or suspensions, etc., containing the compounds of the present invention are employed. (For purposes of this application, topical application shall include mouthwashes and gargles.)

The compounds of the present invention can also be administered in the form of

25 liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multilamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolisable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilisers, preservatives, excipients and the like. The preferred lipids

30 are the phospholipids and phosphatidyl cholines, both natural and synthetic. Methods to form liposomes are known in the art.

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The pharmaceutical composition and method of the present invention may further comprise other therapeutically active compounds as noted herein which are usually applied in the treatment of the above mentioned pathological conditions. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

10 Examples of other therapeutic agents include the following:

cyclosporins (e.g., cyclosporin A), CTLA4-Ig, antibodies such as ICAM-3, anti-IL-2 receptor (Anti-Tac), anti-CD45RB, anti-CD2, anti-CD3 (OKT-3), anti-CD4, anti-CD80, anti-CD86, agents blocking the interaction between CD40 and gp39, such as antibodies specific for CD40 and/or gp39 (i.e., CD154), fusion proteins constructed from CD40 and gp39 (CD40lg and CD8gp39), inhibitors, such as nuclear translocation inhibitors, of NF-kappa B function, such as deoxyspergualin (DSG), cholesterol biosynthesis inhibitors such as HMG-CoA reductase inhibitors (lovastatin and simvastatin), non-steroidal antiinflammatory drugs (NSAIDs) such as ibuprofen, aspirin, acetaminophen and cyclooxygenase inhibitors such as rofecoxib, steroids such as prednisolone or dexamethasone, gold compounds, antiproliferative agents such as methotrexate, FK506 (tacrolimus, Prograf), mycophenolate mofetil, cytotoxic drugs such as azathioprine, VP-16, etoposide, fludarabine, cisplatin and cyclophosphamide, TNF- inhibitors such as tenidap, anti-TNF antibodies or soluble TNF receptor, and rapamycin (sirolimus or Rapamune) or derivatives thereof.

20 When other therapeutic agents are employed in combination with the compounds of the present invention they may be used for example in amounts as noted in the Physician Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

25 In the treatment or prevention of conditions which require protein tyrosine kinase inhibition an appropriate dosage level will generally be about 0.01 to 500 mg per kg patient body weight per day which can be administered in single or multiple doses. Preferably, the dosage level will be about 0.1 to about 250 mg/kg per day; more

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preferably about 0.5 to about 100 mg/kg per day. A suitable dosage level may be about 0.01 to 250 mg/kg per day, about 0.05 to 100 mg/kg per day, or about 0.1 to 50 mg/kg per day. Within this range the dosage may be 0.05 to 0.5, 0.5 to 5 or 5 to 50 mg/kg per day. For oral administration, the compositions are preferably provided in the form of tablets 5 containing 1.0 to 1000 milligrams of the active ingredient, particularly 1.0, 5.0, 10.0, 15.0, 20.0, 25.0, 50.0, 75.0, 100.0, 150.0, 200.0, 250.0, 300.0, 400.0, 500.0, 600.0, 750.0, 800.0, 900.0, and 1000.0 milligrams of the active ingredient for the symptomatic adjustment of the dosage to the patient to be treated. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

10 It will be understood, however, that the specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular 15 condition, and the host undergoing therapy.

Throughout this specification the word "comprise", or variations such as "comprises" or "comprising", will be understood to imply the inclusion of a stated element, integer or step, or group of elements, integers or steps, but not the exclusion of any other element, integer or step, or group of elements, integers or steps.

20 All publications mentioned in this specification are herein incorporated by reference. Any discussion of documents, acts, materials, devices, articles or the like which has been included in the present specification is solely for the purpose of providing a context for the present invention. It is not to be taken as an admission that any or all of these matters form part of the prior art base or were common general knowledge in the field relevant to 25 the present invention as it existed in Australia before the priority date of each claim of this application.

In order that the nature of the present invention may be more clearly understood preferred forms thereof will now be described by reference to the following non-limiting Examples.

30 EXAMPLES

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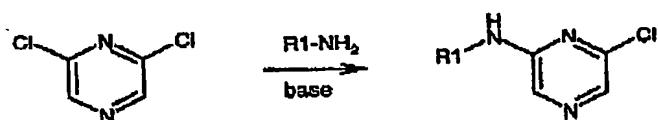
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MATERIALS AND METHODS:

Compound Synthesis

Compounds are generally prepared in a 2-step process starting from 2,6-dichloropyrazine.

5 The first step is a nucleophilic aromatic substitution to generate a monoamino-monohalo intermediate. (Scheme 1).



Scheme 1

10 The nucleophilic aromatic substitution is typically carried out by addition of a primary amine to the di-halogenated heterocycle in a solvent such as ethanol, isopropanol, tert-butanol, dioxane, THF, DMF, toluene or xylene. The reaction is typically performed at elevated temperature in the presence of excess amine or a non-nucleophilic base such as triethylamine or diisopropylethylamine, or an inorganic base such as potassium carbonate or sodium carbonate.

15 Alternatively, the amino substituent may be introduced through a transition metal catalysed amination reaction. Typical catalyst systems for such transformations include $\text{Pd}(\text{OAc})_2/\text{P}(\text{t-Bu})_3$, $\text{Pd}_2(\text{dba})_3/\text{BINAP}$ and $\text{Pd}(\text{OAc})_2/\text{BINAP}$.

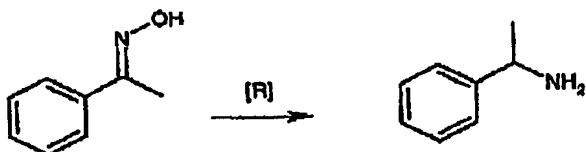
20 The amines employed in the first step of the synthesis of these compounds are obtained commercially or are prepared using methods well known to those skilled in the art. Of particular interest are -methylbenzylamines which are obtained commercially or may be prepared through reduction of oximes (Scheme 2). Typical reductants include lithium aluminium hydride, hydrogen gas in the presence of catalytic palladium on charcoal, Zn in the presence of hydrochloric acid, sodium borohydride in the presence of a Lewis acid such as TiCl_4 , ZrCl_4 , NiCl_2 and MoO_3 , or sodium borohydride in conjunction with 25 Amberlyst H15 ion exchange resin and LiCl . The oximes are obtained in one-step from the corresponding ketones through condensation with hydroxylamine. This reaction is

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generally performed in a protic solvent such as water or ethanol, at temperatures from 0°C to reflux. The hydroxylamine is generally used in the form of its hydrochloride salt, and therefore the reaction is performed in the presence of a base such as sodium hydroxide. The ketones employed as starting materials are generally obtained

5 commercially or via procedures well known to those skilled in the art.



Scheme 2

alpha-Methyl benzylamines of high optical purity may be prepared from chiral alpha-methyl benzyl alcohols using methods well known to those skilled in the art. Such methods

10 include derivatisation of the hydroxyl as a mesylate or tosylate and displacement with a nitrogen nucleophile, such as phthalimide or azide which can then be converted to the primary amine using conventional synthetic methods; or, displacement of the hydroxyl with a suitable nitrogen nucleophile under Mitsunobu conditions. The chiral alpha-methyl benzyl alcohols may be obtained through chiral reduction of the corresponding ketones.

15 Chiral reducing methods are now well known in organic chemistry and include enzymatic processes, asymmetric hydrogenation procedures and chiral oxazaborolidines.

The second step of the synthesis involves a nucleophilic aromatic substitution reaction of the monochloro- mono-amino pyrazine with benzimidazole or indazole. The reaction is typically performed using a salt of the benzimidazole or indazole in solvents such as

20 tetrahydrofuran, dimethylformamide, toluene, or xylene from room temperature to reflux. The benzimidazole or indazole salt is prepared by reaction with a metal hydride such as sodium or potassium hydride or by reaction with caesium carbonate.

Alternatively, a metal-catalysed coupling reaction can be used to introduce the benzimidazole or indazole ring. The reaction is typically performed using a base such as

25 caesium carbonate, rubidium carbonate, potassium carbonate, sodium tert-butoxide or potassium phosphate in a solvent such as xylene, toluene, and DMF from room temperature to reflux. Auxiliary reagents such as phase transfer agents (e.g. cetyltrimonium

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bromide) or copper complexing agents (e.g. phenanthroline) may also be employed in the reaction.

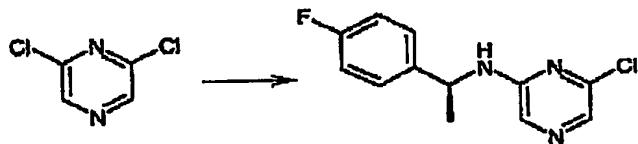
The benzimidazole or indazole components used in this reaction are obtained commercially or are prepared from commercially available benzimidazoles or indazoles 5 via techniques well known to those skilled in the art.

Alternatively, a benzimidazole or indazole derivative may be reacted with the mono-amino mono-chloro pyrazine and the subsequent product further derivatised using methods well known to those skilled in the art.

Representative syntheses are reported below.

10 Example 1

*6-Chloro-N-[(1*S*)-1-(4-fluorophenyl)ethyl]pyrazin-2-amine*



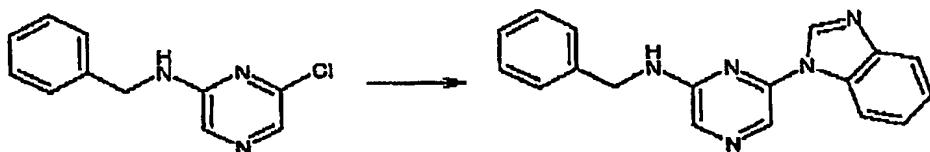
A solution of *S*(-)1-(4-fluorophenyl)-ethylamine (5.0 g, 35.9 mmol), 2,6-dichloropyrazine 15 (5.90 g, 39.6 mmol), diisopropylethylamine (12.5 mL, 71.8 mmol) in ethoxyethanol (25 mL) was heated at 135°C under N₂ overnight. The solvent was removed *in vacuo* and the residue washed with H₂O (2 x 30 mL) and dried (Na₂SO₄). The solvent was removed under reduced pressure and the residue triturated with hexanes (2 x 10 mL) to give a light brown solid. The washings were combined, concentrated and the residue obtained chromatographed using ethyl acetate-hexane (1:4 – 1:2) to separate solid product which, 20 combined with the original solids, gave the total product (7.07 g, 78%).

¹H-n.m.r. (CDCl₃) δ1.56 (d, 3H, *J* = 6.8 Hz, CH₃), 4.81-4.94 (m, 1H, CH), 5.05 (m, 1H, NH), 6.98-7.07 (m, 2H, ArH), 7.29-7.36 (m, 2H, ArH), 7.60 (s, 1H, pyraz-H), 7.80 (s, 1H, pyraz-H).

Example 2

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6-(1H-Benzimidazol-1-yl)-N-benzylpyrazin-2-amine

To a stirred solution of benzimidazole (130 mg, 1.1 mmol) in anhydrous DMF (5 mL) at 0°C under N₂ was added sodium hydride (56 mg, 60% dispersion in oil, 1.45 mmol) in portions over 2 min. The mixture was stirred at 0°C for 15 min and at RT for 60 min. To this was added a solution of (6-chloro-pyrazin-2-yl)-(1-benzyl)-amine (220 mg) in DMF (5 mL) and the resulting mixture was then heated at reflux for 18h. The DMF was removed under reduced pressure and the residue diluted with chloroform. The organic layer was washed with water, dried (Na₂SO₄) and the solvent removed under reduced pressure to furnish the crude product. Column chromatography using dichloromethane-methanol (20:1 → 10:1) as eluant separated the product (100mg).

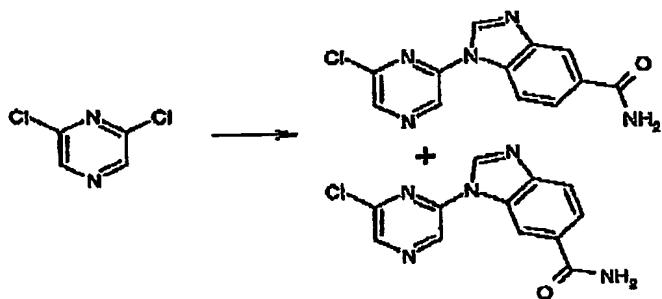
¹H-n.m.r. (CDCl₃) δ4.66 (d, 2H, *J*=5.7Hz, CH₂), 5.56 (m, 1H, NH), 7.29-7.39 (m, 7H, ArH), 7.78-7.89 (m, 2H, ArH), 7.92 (s, 1H, pyraz-H), 8.16 (s, 1H, pyraz-H), 8.48 (s, 1H, ArH2).

m/z (ES) 302 (M⁺+H).

15 Example 3

1-(6-Chloropyrazin-2-yl)-1H-benzimidazole-5-carboxamide and

1-(6-chloropyrazin-2-yl)-1H-benzimidazole-6-carboxamide



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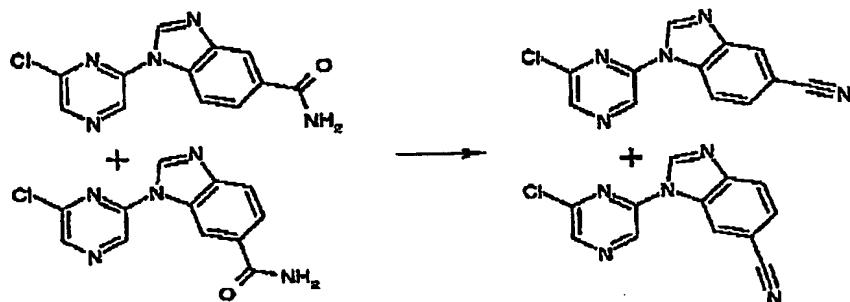
A mixture of 2,6-dichloropyrazine (2.0 g, 13.4 mmol), 1H-benzimidazole-5-carboxamide (2.0 g, 12.3 mmol) and cesium carbonate (5.6 g, 17.2 mmol) in DMF (10 mL) was heated at 90°C for 3h. The solution was cooled to RT and diluted with ethyl acetate (20 mL) and filtered. The solid material was washed with chloroform-methanol (20mL, 4:1) and the 5 combined filtrates concentrated *in vacuo*. The residue thus obtained (3.02 g) was used without further purification.

m/z (EI) 273/275 (M+1)

Example 4

1-(6-Chloropyrazin-2-yl)-1H-benzimidazole-5-carbonitrile and

10 *1-(6-chloropyrazin-2-yl)-1H-benzimidazole-6-carbonitrile*



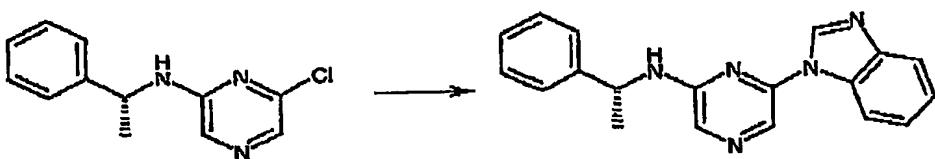
An approximately 1:1 mixture of 1-(6-chloropyrazin-2-yl)-1H-benzimidazole-5-carboxamide and 1-(6-chloropyrazin-2-yl)-1H-benzimidazole-6-carboxamide (0.3 g, 1.09 mmol) and thionyl chloride (0.3 mL, 3.3 mmol) in benzene (3 mL) was heated under reflux 15 overnight. Upon cooling to RT the solution was poured onto ice and the resultant mixture basified to pH ~11 with solid Na₂CO₃. The mixture was then extracted with ethyl acetate (2 x 20 mL) and the combined organic layers washed with brine and dried (Na₂SO₄). The solvent was removed *in vacuo* and the residue purified by column chromatography using dichloromethane-methanol (100:0 – 96:4) as eluant to give the 20 desired product as a mixture of isomers (135 mg).

m/z (EI) 255/257 (M+1)

Example 5

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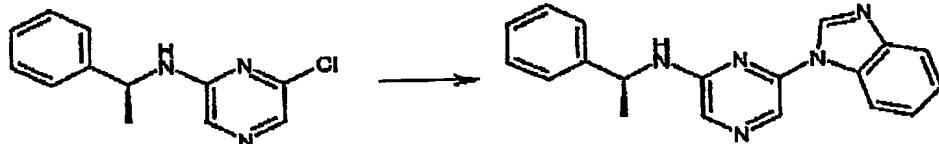
*6-(1*H*-Benzimidazol-1-yl)-N-[(*IR*)-1-phenylethyl]pyrazin-2-amine*

In a procedure analogous to example 2, reaction of 6-chloro-N-[(1*R*)-1-phenylethyl]pyrazin-2-amine (240mg, 1.03mmol) and benzimidazole (130mg, 1.10mmol) furnished the product (187mg, 59%).

¹H-n.m.r. (CDCl₃) δ1.63 (d, 3H, *J*=6.6Hz, CH₃), 4.98-5.20 (m, 1H, CH), 5.58 (d, 1H, *J*=6.0Hz, NH), 7.25-7.42 (m, 6H, Ph-H, ArH), 7.70 (dd, 1H, *J*=7.2, 1.0Hz, ArH), 7.82 (dd, 1H, *J*=8.0, 1.2Hz, ArH), 7.87 (s, 1H, pyraz-H), 8.11 (s, 1H, pyraz-H), 8.38 (s, 1H, ArH).

m/z (ES) 315 (M⁺+H), 212, 105.

10 Example 6

*6-(1*H*-Benzimidazol-1-yl)-N-[(*IS*)-1-phenylethyl]pyrazin-2-amine*

In a procedure analogous to example 2, reaction of 6-chloro-N-[(1*S*)-1-phenylethyl]pyrazin-2-amine (140 mg, 0.60 mmol) and benzimidazole (78 mg, 0.66 mmol) furnished the product (71 mg, 38%).

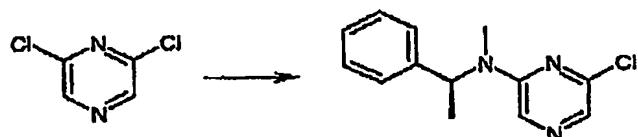
¹H-n.m.r. (CDCl₃) δ1.57 (d, 3H, *J*=6.9Hz, CH₃), 4.95 (m, 1H, CH), 5.29 (d, 1H, *J*=6.0Hz, NH), 7.19-7.35 (m, 7H, Ph-H, ArH), 7.63-7.66 (m, 1H, ArH), 7.74-7.77 (m, 1H, ArH), 7.78 (s, 1H, pyraz-H), 8.06 (s, 1H, pyraz-H), 8.31 (s, 1H, ArH).

m/z (ES) 316 (M⁺+H), 212, 105

20 Example 7

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31.

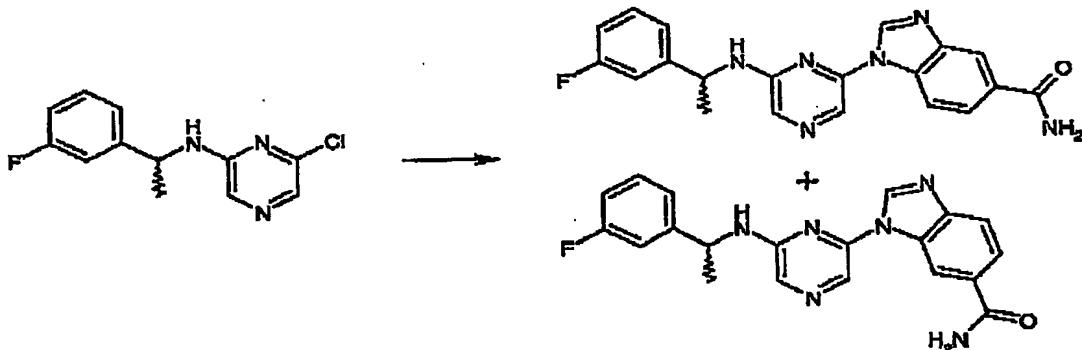
*6-Chloro-N-methyl-N-[(1*S*)-1-phenylethyl]pyrazin-2-amine*

In an analogous fashion to example 1, N-methyl-N-[(1*S*)-1-phenylethyl]amine (0.27 g, 2.0 mmol) was condensed with 2,6-dichloropyrazine (0.36 g, 2.4 mmol), to furnish the desired 5 product as a light brown solid (192 mg, 39%).

¹H-n.m.r. (CDCl₃) δ1.56 (d, 3H, *J*= 6.8 Hz, CH₃), 4.81-4.94 (m, 1H, CH), 5.05 (m, 1H, NH), 6.98-7.07 (m, 2H, ArH), 7.29-7.36 (m, 2H, ArH), 7.60 (s, 1H, pyraz-H), 7.80 (s, 1H, pyraz-H).

Example 8

10 *1-(6-[(1-(3-Fluorophenyl)ethyl]amino)pyrazin-2-yl)-1H-benzimidazole-6-carboxamide* and *1-(6-[(1-(3-fluorophenyl)ethyl]amino)pyrazin-2-yl)-1H-benzimidazole-6-carboxamide*



In an analogous fashion to Example 3, 6-chloro-N-[1-(3-fluorophenyl)ethyl]pyrazin-2-amine (0.25 g, 1 mmol) was reacted with 1H-benzimidazole-5-carboxamide (0.2 g, 1.2 mmol) to afford the product as a mixture of isomers. These were separated by chromatography using dichloromethane-methanol (98:2 - 92:8) as eluant to afford from the less polar fractions 1-(6-[(1-(3-fluorophenyl)ethyl]amino)pyrazin-2-yl)-1H-benzimidazole-6-carboxamide (80 mg).

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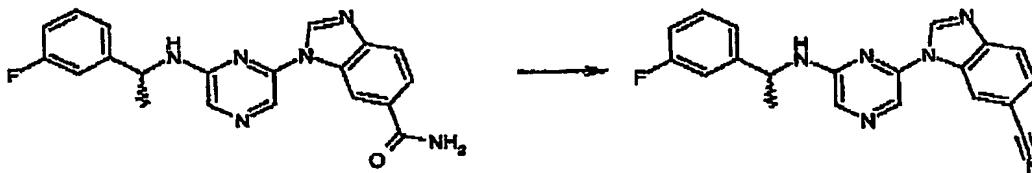
¹H-n.m.r. (CDCl₃) δ1.64 (d, 3H, J= 6.8 Hz, CH₃), 4.97-5.10 (m, 1H, CH), 5.47 (d, 1H, J= 6.2 Hz, NH), 6.90-6.99 (m, 1H, ArH), 7.09-7.38 (m, 3H, ArH), 7.72 (dd, 1H, J= 8.4, 1.6 Hz, ArH), 7.86 (s, 1H, pyraz-H), 7.87 (d, 1H, J= 8.4 Hz, ArH), 8.22 (s, 1H, pyraz-H), 8.47 (s, 1H, ArH), 8.60 (d, 1H, J= 1.6 Hz, ArH).

5 From the more polar fractions was isolated 1-(6-[(1-(3-fluorophenyl)ethyl]amino)pyrazin-2-yl)-1H-benzimidazole-5-carboxamide (63 mg).

10 ¹H-n.m.r. (CDCl₃) δ1.63 (d, 3H, J= 6.8 Hz, CH₃), 4.94-5.07 (m, 1H, CH), 5.44 (d, 1H, J= 6.6 Hz, NH), 6.90-7.38 (m, 4H, ArH), 7.65 (d, 1H, J= 9.0 Hz, ArH), 7.82 (dd, 1H, J= 8.8, 1.6 Hz, ArH), 7.93 (s, 1H, pyraz-H), 8.13 (s, 1H, pyraz-H), 8.25 (d, 1H, J= 1.4 Hz, ArH), 8.41 (s, 1H, ArH).

Example 9

1-(6-[(1-(3-Fluorophenyl)ethyl]amino)pyrazin-2-yl)-1H-benzimidazole-6-carbonitrile



15 In an analogous procedure to that reported in Example 4, 1-(6-[(1-(3-fluorophenyl)ethyl]amino)pyrazin-2-yl)-1H-benzimidazole-6-carboxamide (80 mg, 0.21 mmol) was reacted with phosphorus oxychloride to afford the product as a pale yellow solid (60 mg, 80%).

20 ¹H-n.m.r. (CDCl₃) δ1.65 (d, 3H, J= 6.6 Hz, CH₃), 4.94-5.09 (m, 1H, CH), 5.57 (d, 1H, J= 6.2 Hz, NH), 6.92-7.12 (m, 2H, ArH), 7.20-7.25 (m, 1H, ArH), 7.35-7.46 (m, 1H, ArH), 7.59 (dd, 1H, J= 8.4, 1.4 Hz, ArH), 7.88 (d, 1H, J= 8.4 Hz, ArH), 7.94 (s, 1H, pyraz-H), 8.12 (s, 1H, pyraz-H), 8.25 (d, 1H, J= 1.4 Hz, ArH), 8.51 (s, 1H, ArH).

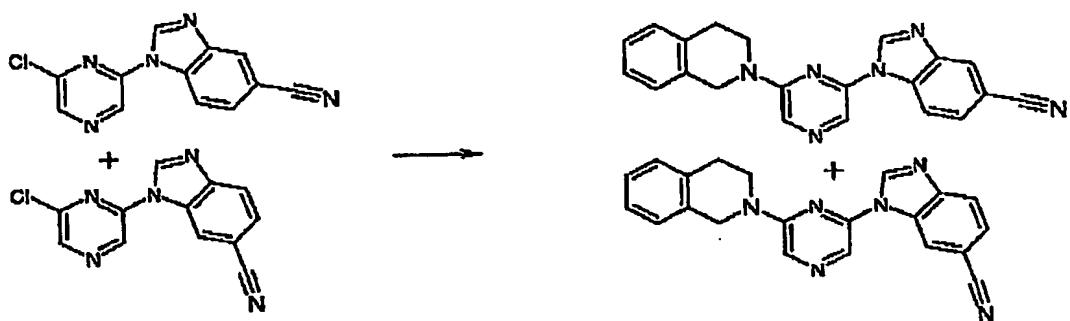
Example 10

1-[6-(3,4-Dihydroisoquinolin-2(1H)-yl)pyrazin-2-yl]-1H-benzimidazole-5-carbonitrile

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33.

and

1-[6-(3,4-dihydroisoquinolin-2(1H)-yl)pyrazin-2-yl]-1H-benzimidazole-6-carbonitrile

In an analogous fashion to Example 1, an approximately 1:1 mixture of 1-(6-chloropyrazin-2-yl)-1H-benzimidazole-5-carbonitrile and 1-(6-chloropyrazin-2-yl)-1H-benzimidazole-6-carbonitrile (102 mg, 0.4 mmol) was condensed with 1,2,3,4-tetrahydroisoquinolinc (64 mg, 0.48 mmol). The crude product was triturated with cold ethyl acetate to separate 1-[6-(3,4-dihydroisoquinolin-2(1H)-yl)pyrazin-2-yl]-1H-benzimidazole-5-carbonitrile as an off-white solid (65 mg)

10 ¹H-n.m.r. (CDCl₃) δ3.05-3.11 (m, 2H, CH₂), 3.95-4.02 (m, 2H, CH₂), 4.85 (m, 2H, CH₂), 7.25-7.29 (m, 3H, ArH), 7.61-7.68 (m, 1H, ArH), 7.95 (d, 1H, *J* = 8.2 Hz, ArH), 8.11-8.21 (m, 1H, ArH), 8.16 (s, 1H, pyraz-H), 8.23 (s, 1H, pyraz-H), 8.38 (m, 1H, ArH), 8.65 (s, 1H, ArH).

15 The ethyl acetate washings were combined and concentrated *in vacuo* to furnish 1-[6-(3,4-dihydroisoquinolin-2(1H)-yl)pyrazin-2-yl]-1H-benzimidazole-6-carbonitrile (41 mg) ¹H-n.m.r. (CDCl₃) δ3.07 (t, 2H, *J* = 5.9 Hz, CH₂), 3.97 (t, 2H, *J* = 6.1 Hz, CH₂), 4.84 (s, 2H, CH₂), 7.24-7.32 (m, 4H, ArH), 7.67 (dd, 1H, *J* = 8.8, 1.4 Hz, ArH), 8.11-8.21 (m, 1H, ArH), 8.16 (s, 1H, pyraz-H), 8.22 (s, 1H, pyraz-H), 8.65 (s, 1H, ArH).

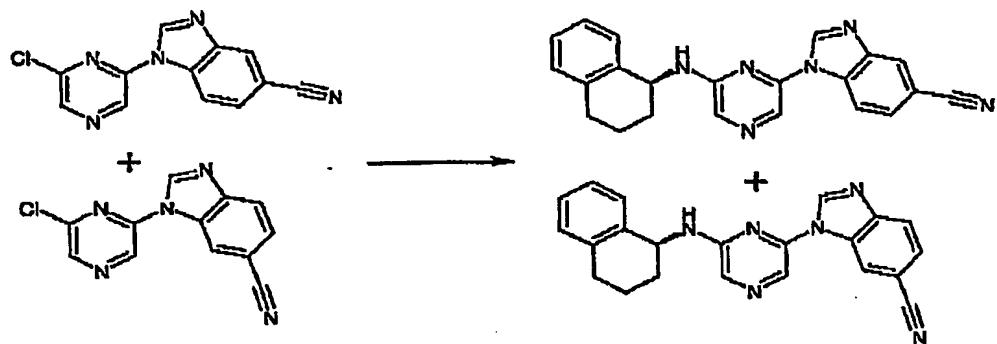
Example 11

20 *1-[6-[(1S)-1,2,3,4-Tetrahydronaphthalen-1-ylamino]pyrazin-2-yl]-1H-benzimidazole-5-carbonitrile* and

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34.

1-[6-[(1S)-1,2,3,4-tetrahydronaphthalen-1-ylamino]pyrazin-2-yl]-1H-benzimidazole-6-carbonitrile



In an analogous fashion to Example 1, an approximately 1:1 mixture of 1-(6-chloropyrazin-2-yl)-1H-benzimidazole-5-carbonitrile and 1-(6-chloropyrazin-2-yl)-1H-benzimidazole-6-carbonitrile (100 mg, 0.39 mmol) was condensed with (1S)-1,2,3,4-tetrahydronaphthalen-1-amine (69 mg, 0.47 mmol). The product was obtained as a mixture of regioisomers which were separated by column chromatography using dichloromethane-methanol (95:5) as eluant. From the less polar fractions 1-[6-[(1S)-1,2,3,4-tetrahydronaphthalen-1-ylamino]pyrazin-2-yl]-1H-benzimidazole-6-carbonitrile was obtained as a yellow semi-solid (26 mg).

¹H-n.m.r. (CDCl₃) δ1.87-1.98 (m, 2H, CH₂), 2.04-2.18 (m, 2H, CH₂), 2.82-2.90 (m, 2H, CH₂), 5.18-5.30 (m, 2H, NH + CH), 7.14-7.23 (m, 3H, ArH), 7.32-7.38 (m, 1H, ArH), 7.61 (dd, 1H, J = 8.2, 1.4 Hz, ArH), 7.94 (s, 1H, pyraz-H), 8.11 (d, 1H, J = 8.2 Hz, ArH), 8.14 (s, 1H, pyraz-H), 8.18 (d, 1H, J = 1.4 Hz, ArH), 8.61 (s, 1H, ArH).

From the more polar fractions was isolated 1-[6-[(1S)-1,2,3,4-tetrahydronaphthalen-1-ylamino]pyrazin-2-yl]-1H-benzimidazole-5-carbonitrile (19 mg)

¹H-n.m.r. (CDCl₃) δ1.89-2.02 (m, 2H, CH₂), 2.10-2.20 (m, 2H, CH₂), 2.83-2.91 (m, 2H, CH₂), 5.25 (m, 2H, NH + CH), 7.15-7.35 (m, 4H, ArH), 7.62 (dd, 1H, J = 8.4, 1.4 Hz, ArH), 7.91-7.95 (m, 2H, ArH + pyraz-H), 8.15 (s, 1H, pyraz-H), 8.52 (br s, 1H, ArH), 8.66 (s, 1H, ArH).

Example 12

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35.

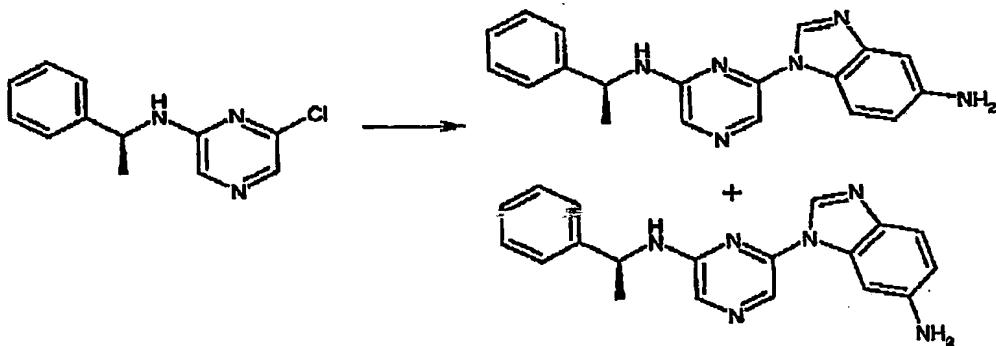
1H-Benzimidazole-5-carboxamide

To a stirred suspension of benzimidazole-5-carboxylic acid (5.0 g, 30.8 mmol) in benzene (25 mL) was added thionyl chloride (25 mL) dropwise at room temperature. To this 5 mixture was added DMF (0.1 mL) and it was then heated under reflux for 6h. Benzene and thionyl chloride was evaporated off under reduced pressure and toluene (20 mL) added to the residue. This was removed under reduced pressure and the acid chloride thus obtained suspended in tetrahydrofuran (20 mL). To this was the added 28% aqueous ammonia (20 mL) dropwise at 0°C, and the resultant mixture was then stirred at room 10 temperature overnight. The precipitate was filtered and washed with cold H₂O to give the primary amide as a brown solid (3.55 g).

¹H-n.m.r. (d₆-DMSO) δ7.25 (br s, 1H, NH), 7.60 (d, 1H, J = 8.4 Hz, ArH), 7.78 (dd, 1H, J = 8.4 and 1.6 Hz, ArH), 7.97 (br s, 1H, CONH), 8.18 (br s, 1H, ArH), 8.32 (br s, 1H, ArH).

Example 13

15 *1-((S)-1-Phenylethyl)amino)pyrazin-2-yl)-1H-benzimidazol-5-amine and 1-((S)-1-phenylethyl)amino)pyrazin-2-yl)-1H-benzimidazol-6-amine*



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36.

To a stirred solution of 5-amino-benzimidazole (290 mg, 2.2 mmol) in anhydrous DMF (10 mL) under N₂ was added caesium carbonate (980 mg). The resulting mixture was stirred at 70°C for 60 min. To this was added a solution of

6-chloro-N-[(1S)-1-phenylethyl]pyrazin-2-amine (470 mg) in DMF (5 mL) and the

5 resulting mixture was then heated at reflux for 48h. The DMF was removed under reduced pressure and the residue diluted with chloroform. The organic layer was washed with aqueous Na₂CO₃, dried (Na₂SO₄) and the solvent removed under reduced pressure to furnish the crude product. Column chromatography using dichloromethane-methanol (95:5 - 92:8) as eluant separated two fractions from unreacted starting material. The 10 higher R_f fraction was assigned as the 6-isomer (276mg, 42%).

¹H-n.m.r. (CDCl₃) δ1.64 (d, 3H, *J*= 6.9Hz, CH₃), 2.90 (br s, 2H, NH₂), 5.05 (m, 1H, CH), 5.21 (d, 1H, NH), 6.70 (dd, 1H, *J*= 8.7, 2.1Hz, ArH), 6.97 (d, 1H, *J*= 1.8Hz, ArH), 7.28-7.43 (m, 5H, Ph-H), 7.58 (d, 1H, *J*= 8.4Hz, ArH), 7.84 (s, 1H, pyraz-H), 8.08 (s, 1H, pyraz-H), 8.21 (s, 1H, ArH). *m/z* (ES) 331 (M⁺+H).

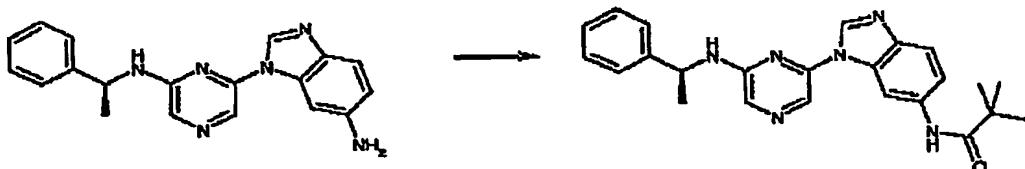
15 The lower fraction was assigned as the 5-isomer (170mg, 26%).

¹H-n.m.r. (CDCl₃) δ1.64 (d, 3H, *J*= 6.9Hz, CH₃), 2.85 (br s, 2H, NH₂), 5.01 (m, 1H, CH), 5.19 (d, 1H, NH), 6.70 (dd, 1H, *J*= 8.7, 2.1Hz, ArH), 7.11 (d, 1H, *J*= 1.8Hz, ArH), 7.29-7.40 (m, 5H, Ph-H), 7.51 (d, 1H, *J*= 8.7Hz, ArH), 7.81 (s, 1H, pyraz-H), 8.10 (s, 1H, pyraz-H), 8.32 (s, 1H, ArH).

20 *m/z* (ES) 331 (M⁺+H).

Example 14

N-[(1-(6-[(1S)-1-phenylethyl]amino)pyrazin-2-yl)-1H-benzimidazol-5-yl]-2,2-dimethylpropanamide



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37.

To a stirred solution of 2-(benzylamino)-6-(5-amino-benzimidazo-1-yl)-pyrazine (33 mg, 0.1mmol) in anhydrous THF (2 mL) under N₂ was added triethylamine (38 μ L, 0.3 mmol). The solution was cooled at 0°C and to this was added pivalic acid (12 mg, 0.11 mmol) and EDC (23 mg, 0.12 mmol) and the resulting mixture then stirred at RT. After 64h the 5 solution was diluted with H₂O and the mixture extracted with CHCl₃ (2 x 15 mL). The combined organic layers were washed with 10% aqueous Na₂CO₃, dried (Na₂SO₄) and the solvent removed in vacuo. The residue was purified by column chromatography using dichloromethane-methanol (100:6) as eluant to separate the pure product (15mg).

15 ¹H-n.m.r. (CDCl₃) δ 1.35 (s, 9H, 3CH₃), 1.65 (d, 3H, J = 6.6Hz, CH₃), 5.14 (m, 1H, CH), 5.24 (d, 1H, J = 5.7Hz, NH), 7.13 (d, 1H, J = 8.7 Hz, ArH), 7.29-7.47 (m, 5H, ArH), 7.75 (d, 1H, J = 8.7 Hz, ArH), 7.81 (s, 1H, pyraz-H), 8.17 (s, 1H, pyraz-H), 8.35 (s, 1H, ArH), 8.69 (s, 1H, CONH).

Example 15

*N-[1-(6-[(*S*)-1-Phenylethyl]amino)pyrazin-2-yl]-1H-benzimidazol-5-yl]acetamide*



15

To a stirred solution of 2-(*S*- α -methylbenzylamino)-6-(5-amino-benzimidazo-1-yl)-pyrazine (66 mg, 0.2 mmol) in anhydrous THF (2 mL) under N₂ was added triethylamine (41 mg, 0.4 mmol). The solution was cooled at 0°C and to this was added acetyl chloride (17 mg, 0.22 mmol) and the resulting mixture then stirred at RT. 20 After 18h the solution was poured into water (30 mL) and the product extracted into chloroform (2 x 20 mL). The combined organic layers were dried (Na₂SO₄) and the solvent removed under reduced pressure to furnish the crude product as a pale yellow solid. Column chromatography using dichloromethane-methanol (200:15) as eluant separated the product as a pale yellow solid (38 mg).

25 ¹H-n.m.r. (CDCl₃) δ 1.63 (d, 3H, J = 6.6Hz, CH₃), 2.21 (s, 3H, CH₃), 5.00 (m, 1H, CH), 5.43 (d, 1H, J = 5.7Hz, NH), 7.27-7.38 (m, 5H, ArH), 7.49 (d, 1H, J = 9.0Hz, ArH), 7.61 (d, 1H, J =

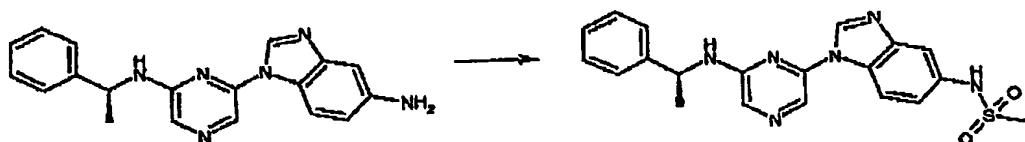
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38.

9.0Hz, ArH), 7.74 (br s, 1H, CONH), 7.84 (s, 1H, pyraz-H), 7.90 (s, 1H, ArH), 8.11 (s, 1H, pyraz-H), 8.36 (s, 1H, ArH).

Example 16

N-[1-[(6-[(1S)-1-Phenylethyl]amino)pyrazin-2-yl]-1H-benzimidazo-5-yl]methanesulfonamide



To a stirred solution of 2-(*S*- α -methylbenzylamino)-6-(5-amino-benzimidazo-1-yl)-pyrazine (33 mg, 0.1 mmol) in anhydrous THF (2 mL) under N_2 was added triethylamine (40 mg, 0.4 mmol). The solution was cooled at 0°C and to this was added 10 methanesulphonyl chloride (25 mg, 0.2 mmol) and the resulting mixture then stirred at RT. After 16h the solution was poured into water (30 mL) and the product extracted into chloroform (2 x 15 mL). The combined organic layers were washed with 10% Na_2CO_3 , dried (Na_2SO_4) and the solvent removed under reduced pressure to furnish the crude product as a pale yellow solid. Column chromatography, using dichloromethane-methanol (100:6) as eluant, separated the product from the most polar fractions as a pale yellow solid (16mg).

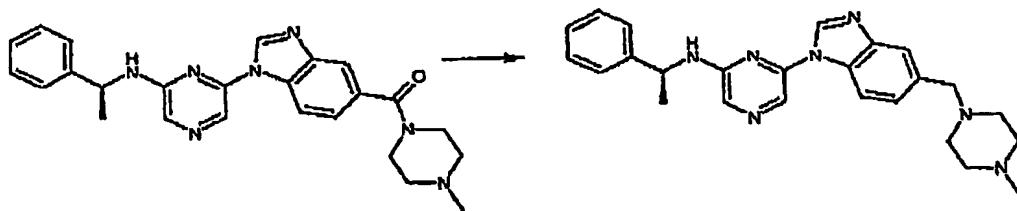
¹H-n.m.r. ($CDCl_3$) 81.65 (d, 3H, J = 6.9 Hz, CH_3), 3.00 (s, 3H, CH_3), 5.02 (m, 1H, CH), 5.27 (d, 1H, J = 6.0 Hz, NH), 7.21-7.40 (m, 6H, ArH), 7.64 (d, 1H, J = 8.7 Hz, ArH), 7.69 (d, 1H, J = 1.9 Hz, ArH), 7.88 (s, 1H, pyraz-H), 8.10 (s, 1H, pyraz-H), 8.41 (s, 1H, ArH).

20 Example 17

*2-(*S*- α -Methylbenzylamino)-6-(*N*-methylpiperazin-4-yl-methyl)-benzimidazo-1-yl)pyrazine*

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39.



A solution of

3-[6-(S-a-methylbenzylamino)-pyrazin-2-yl]-3H-benzimidazole-5-carboxylic acid

N-methylpiperazinylamide (22mg, 0.05mmol) in dry THF (1mL) was added to a

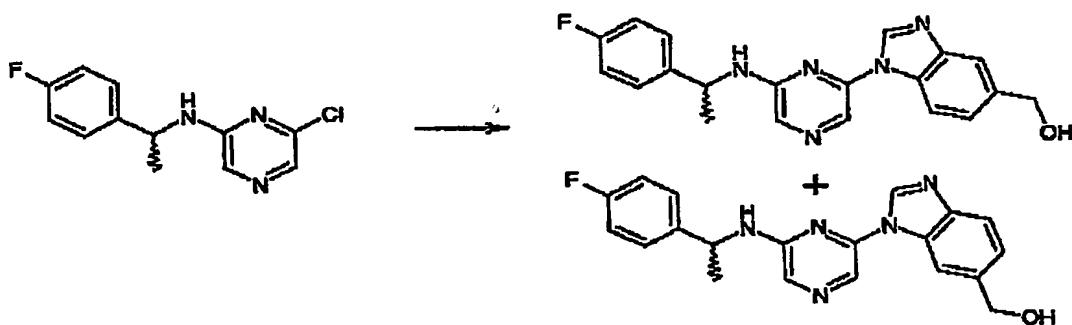
5 suspension of LiAlH₄ (4mg, 0.1mmol) in THF (1mL) and the mixture heated at reflux for 4h. Upon cooling to RT, the solution was treated consecutively with H₂O (1mL), aqueous NaOH (1mL, 2M) and H₂O (5mL). The resulting mixture was extracted with CHCl₃ (2 x 10mL) and the combined organic layers dried (Na₂SO₄). The solvent was removed under reduced pressure and the product purified by flash chromatography using CH₂Cl₂-MeOH (10:1 → 1:1) as eluant to afford the product as a yellow solid (11mg, 52%).

¹H-n.m.r. (CDCl₃) δ1.65 (d, 3H, *J*= 6.9Hz, CH₃), 2.58 (s, 3H, NCH₃), 2.81 (br s, 4H, CH₂), 2.90 (br s, 4H, CH₂), 3.74 (s, 2H, NCH₂), 5.03 (m, 1H, CH), 5.33 (d, 1H, *J*= 6.0 Hz, NH), 7.25-7.42 (m, 6H, ArH), 7.67 (d, 1H, *J*= 8.4 Hz, ArH), 7.77 (s, 1H, ArH), 7.87 (s, 1H, pyraz-H), 8.12 (s, 1H, pyraz-H), 8.39 (s, 1H, ArH).

15 Example 18

[1-(6-[(1-(4-Fluorophenyl)ethyl]amino)pyrazin-2-yl]-1H-benzimidazol-5-yl]methanol and

[1-(6-[(1-(4-fluorophenyl)ethyl]amino)pyrazin-2-yl]-1H-benzimidazol-6-yl]methanol



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40.

In a procedure analogous to Example 3, reaction of 6-chloro-N-[1-(4-fluorophenyl)ethyl]pyrazin-2-amine (1.80 g, 7.15 mmol) and 5-hydroxymethyl benzimidazole (1.26 g, 8.5 mmol) furnished the two products which were separated by column chromatography using dichloromethane-methanol (98:2 – 92:8) as eluant. From 5 the less polar fractions was obtained [1-(6-[(1-(4-fluorophenyl)ethyl]amino)pyrazin-2-yl]-1H-benzimidazol-5-yl]methanol as a pale yellow solid (210 mg).

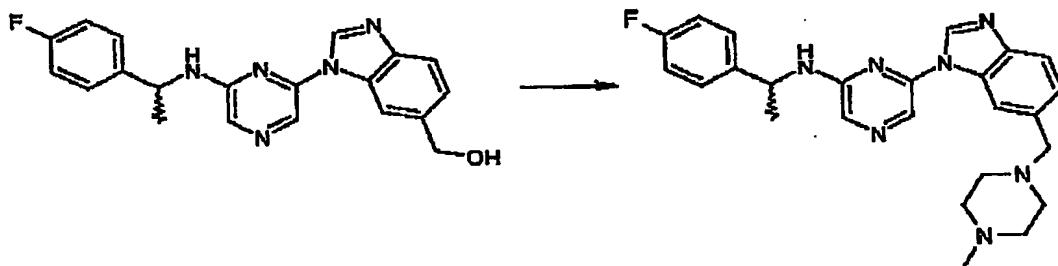
¹H-n.m.r. (CDCl₃) δ1.60 (d, 3H, *J* = 6.8 Hz, CH₃), 4.93-5.05 (m, 1H, CH), 5.48 (d, 1H, *J* = 6.2 Hz, NH), 6.97-7.07 (m, 2H, ArH), 7.29-7.39 (m, 3H, ArH), 7.76 (d, 1H, *J* = 9.4 Hz, ArH), 7.79 (s, 1H, pyraz-H), 7.89 (s, 1H, ArH), 8.09 (s, 1H, pyraz-H), 8.34 (s, 1H, ArH).

10 From the more polar fractions was isolated [1-(6-[(1-(4-fluorophenyl)ethyl]amino)pyrazin-2-yl]-1H-benzimidazol-5-yl]methanol as a yellow solid (265 mg).

¹H-n.m.r. (CDCl₃) δ1.62 (d, 3H, *J* = 6.8 Hz, CH₃), 4.82 (s, 2H, CH₂OH), 4.94-5.06 (m, 1H, CH), 5.29 (d, 1H, *J* = 6.0 Hz, NH), 7.02-7.10 (m, 2H, ArH), 7.29-7.40 (m, 3H, ArH), 7.68 (d, 1H, *J* = 8.4 Hz, ArH), 7.80 (d, 1H, *J* = 1.2 Hz, ArH), 7.84 (s, 1H, pyraz-H), 8.12 (s, 1H, pyraz-H), 8.39 (s, 1H, ArH).

Example 19

N-(1-(4-Fluorophenyl)ethyl)-6-[(4-methylpiperazin-1-yl)methyl]-1H-benzimidazol-1-yl]pyrazin-2-amine



20 A solution of the alcohol (0.18 g, 0.5 mmol) in dichloromethane (5 mL) was cooled to 0°C and to this was added diisopropylethylamine (0.13 mL, 0.75 mmol) and methanesulfonyl chloride (46 μL, 0.59 mmol). After stirring at RT for 2h. a further aliquot of diisopropylethylamine (30 μL) and methanesulfonyl chloride (20 μL) was added. After

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41.

1h. H_2O (10 mL) was added and the organic layer collected. The aqueous phase was extracted with dichloromethane (3 x 5 mL) and the organic layers combined, dried (Na_2SO_4) and concentrated *in vacuo*. An aliquot of the crude mesylate thus obtained (100 mg) was dissolved in DMF (2 mL) and to this was added diisopropylethylamine (52 μL , 0.3 mmol) and 1-methylpiperazine (25 μL , 0.45 mmol). The solution was heated at 60°C overnight. The solution was then concentrated *in vacuo* and the residue dissolved in dichloromethane (20 mL) and washed with H_2O . The organic layer was dried (Na_2SO_4) and concentrated and the product purified by chromatography using dichloromethane-methanol-aqueous ammonia (95:5:0 - 95:5:1) to furnish the product as a pale yellow semi-solid (34 mg).

$^1\text{H-n.m.r.}$ (CDCl_3) δ 1.63 (d, 3H, J = 7.2 Hz, CH_3), 2.26 (s, 3H, NCH_3), 2.45 (br s, 8H, 4 \times CH_2), 3.62 (s, 2H, CH_2), 4.99-5.11 (m, 1H, CH), 5.41 (d, 1H, J = 6.4 Hz, NH), 6.99-7.07 (m, 2H, ArH), 7.30-7.41 (m, 3H, ArH), 7.76 (d, 1H, J = 8.4 Hz, ArH), 7.82 (s, 1H, pyraz-H), 7.89 (s, 1H, ArH), 8.17 (s, 1H, pyraz-H), 8.39 (s, 1H, ArH).

15 Example 20

1-Thien-2-ylethanamine



To a solution of 1-thien-2-ylethanone (505 mg, 4 mmol) and ammonium formate (1.26 g, 20 mmol) in methanol (4 mL) under nitrogen was added dichloro(pentamethylcyclopentadienyl)rhodium (III) dimer (14 mg, 0.023 mmol). The solution was heated at reflux for 7 h. after which time the solution was cooled to room temperature and acidified to pH ~2 with 2M HCl. The mixture was washed with dichloromethane (3 x 15 mL) and the aqueous phase then basified to pH ~12 by addition of 5M NaOH. The aqueous phase was extracted with dichloromethane (3 x 15 mL) and the combined organic layers dried (Na_2SO_4) and concentrated to give a pure product (280 mg, 55%).

m/z (EI) 127 (M^+), 112 (M-15)⁺

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42.

SCREENING**JAK Tyrosine Kinase Domain Production****JAK kinase domains were produced in the following manner:****JAK1**

5 The kinase domain of human JAK1 was amplified from U937mRNA using the polymerase chain reaction with the following primers:

XHOI-J1 5'-CCG CTC GAG ACT GAA GTG GAC CCC ACA CAT-3'

J1-KPNI 5'-CGG CGT ACC TTA TTT TAA AAG TGC TTC AAA-3'

10 JAK1 PCR products were cloned into the pFastBac HTb expression vector (Gibco) via the Xho I and Kpn I sites. The JAK1 plasmid was then transformed into competent DH10Bac cells (Gibco), and the recombinant baculovirus produced prepared for transfection into Sf9 insect cells.

JAK2

15 The kinase domain of human JAK2 was amplified from U937mRNA using the polymerase chain reaction with the following primers:

SALL-jk2 5'-ACG CGT CGA CCG TGC CTT TGA AGA CCG GGA T-3'

jk2-NOTI 5'-ATA GTT TAG CCG CCG CTC AGA ATG AAG GTC ATT T-3'

20 JAK2 PCR products were cloned into the pFastBac HTc expression vector (Gibco) via the Sal I and Not I sites. The JAK2 plasmid was then transformed into competent DH10Bac cells (Gibco), and the recombinant baculovirus produced prepared for transfection into Sf9 insect cells.

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43.

JAK3

The kinase domain of human JAK3 was amplified from U937 mRNA using the polymerase chain reaction with the following primers:

XHOI-J3 5'-CCG CTC GAG TAT GCC TGC CAA GAC CCC ACG-3'

5 J3-KPNI 5'-CCG GGT ACC CTA TGA AAA GGA CAG GGA GTG-3'

JAK3 PCR products were cloned into the pFastBac HTb expression vector (Gibco) via the Xho I and Kpn I sites. The JAK3 plasmid was then transformed into competent DH10Bac cells (Gibco), and the recombinant baculovirus produced prepared for transfection into Sf9 insect cells.

10 TYK2

The kinase domain of human TYK2 was amplified from A549 mRNA using the polymerase chain reaction with the following primers:

HT2BK 5'-GGA GCA CTC GAG ATG GTA GCA CAC AAC CAG GTG-3'

ITY2.2R 5'-GGA GCA GGA ATT CCG GCG CTG CCG GTC AAA TCT GG-3'

15 TYK2 PCR products were cloned into pBlueBacHis2A (Invitrogen) via the EcoRI site. The recombinant TYK2 baculovirus produced was prepared for transfected into Sf9 insect cells.

Large Scale Production Of Kinase Domains

Baculovirus preparations from each of the JAK family members were infected into five litres of High Five cells (Invitrogen) grown in High Five serum free medium (Invitrogen) to a cell density of approximately $1-2 \times 10^6$ cells/ml. Cells are infected with virus at a MOI of 0.8-3.0. Cells were harvested and lysed. JAK kinase domains were purified by affinity chromatography on a Probond (Invitrogen) nickel chelate affinity column.

Assay Protocols

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44.

Kinase assays were performed either in a 96 well capture-based ELISA assay or in 384 well Optiplates (Packard) using an Alphascreen Protein Tyrosine Kinase kit. In either case using approximately 1.5 μ g of affinity purified PTK domain in the presence of 50mM HEPES, pH 7.5, 10mM MgCl₂, 150mM NaCl and 10 μ M-1mM ATP. The 5 biotinylated substrate biotin-EGPWLEEEAYGWMDF-NH₂ (final concentration 5 μ M) was used as substrate. In the ELISA assay tyrosine phosphorylation was quantitated following transfer to an avidin coated ELISA plate using peroxidase-linked 10 anti-phospho-tyrosine antibody PY20. In the Alphascreen assay, Alphascreen phosphotyrosine acceptor beads followed by streptavidin donor beads were added under subdued light. The ELISA plates were read on a BMG Fluorostar, the Alphascreen plates were read on a Packard Fusion Alpha. Inhibitors were added to the assays fifteen minutes prior to the addition of ATP. Inhibitors were added in aqueous DMSO, with DMSO concentrations never exceeding 1%.

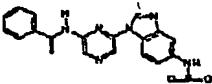
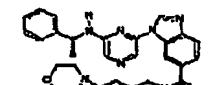
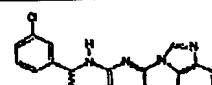
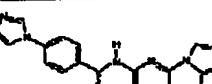
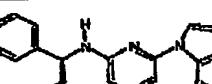
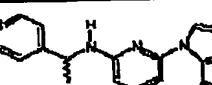
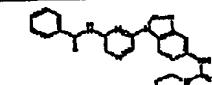
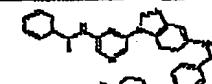
Results

15 The activity of a range of compounds is shown in Table 3. Compounds that exhibited a capacity to inhibit 50% or greater of enzyme activity at a concentration of 20 μ M (measured under standard conditions, see Methods), are designated as "+". Compounds not tested are designated "NT"; while compounds that did not inhibit enzyme activity by 50% at 20 μ M are designated "-".

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45.

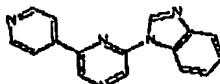
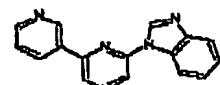
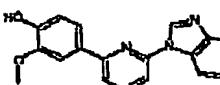
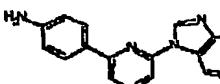
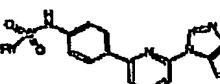
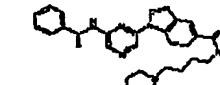
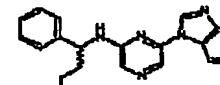
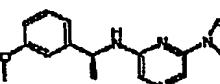
Table 3

CHEMISTRY	Jak2	Jak3	zap70	tie2	hck	abl	fms	kdr	blk
 C25H22N6O2S	+	+	NT	NT	NT	NT	NT	NT	NT
 C28H33N7O2	+	+	+	NT	NT	NT	NT	+	NT
 C19H16CNS	-	-	NT	NT	NT	NT	NT	NT	NT
 C22H19N7	-	-	NT	NT	NT	NT	NT	NT	NT
 C26H19NS	+	-	+	NT	NT	+	NT	NT	NT
 C18H18N8	-	-	NT	NT	NT	NT	NT	+	NT
 C26H20N8O	+	-	+	NT	+	+	NT	+	NT
 C32H34N8O	-	-	+	NT	+	NT	NT	NT	NT

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46.

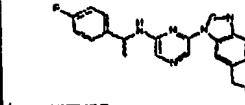
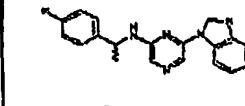
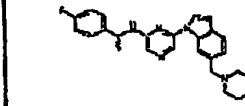
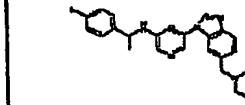
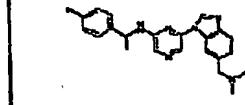
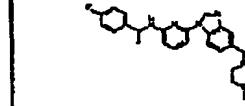
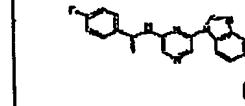
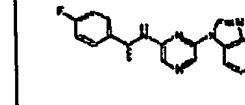
Table 3 (cont.)

CHEMISTRY	jak2	jak3	zap70	ter2	hck	abl	tma	kdr	blk
 C16H11NS	+	-	NT	NT	NT	NT	NT	NT	NT
 C16H11NS	+	-	NT	NT	NT	NT	NT	NT	NT
 C16H14N4O2	-	-	NT	NT	NT	+	NT	NT	NT
 C17H13NS	+	-	+	NT	NT	NT	NT	NT	NT
 C23H17N5O2S	+	+	NT	NT	NT	NT	NT	NT	NT
 C28H39N7O2	+	-	+	NT	NT	+	NT	NT	NT
 C21H21NS	+	-	NT	NT	NT	NT	NT	NT	NT
 C20H19N5O	-	-	NT	NT	NT	NT	NT	+	NT

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47.

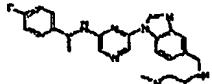
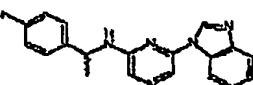
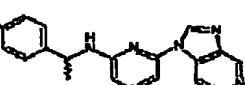
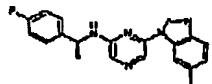
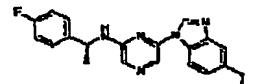
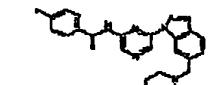
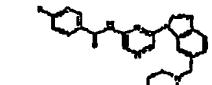
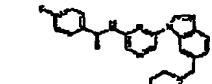
Table 3 (cont.)

CHEMISTRY	Jak2	Jak3	zap70	tie2	hox	abl	fms	kdr	blk
 C20H18FN5O	+	-	NT	NT	NT	NT	NT	+	NT
 C20H18FN5O	-	-	NT	NT	NT	NT	NT	+	NT
 C25H28FN7	-	-	NT	NT	NT	NT	NT	NT	NT
 C24H27FN6	-	-	NT	NT	NT	NT	NT	NT	NT
 C24H28FN7	-	-	NT	NT	NT	NT	NT	+	NT
 C25H28FN7	-	-	NT	NT	NT	NT	NT	+	NT
 C24H27FN6	-	-	NT	NT	NT	NT	NT	+	NT
 C22H23FN8	-	-	NT	NT	NT	NT	NT	+	NT

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48.

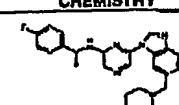
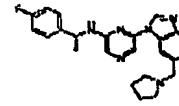
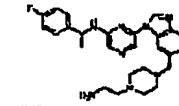
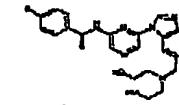
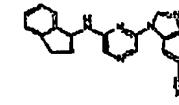
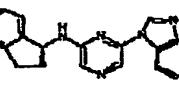
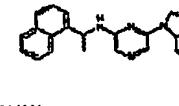
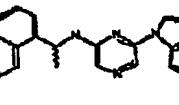
Table 3 (cont.)

CHEMISTRY	Jak2	Jak3	zap70	tie2	hck	abl	fms	kdr	blk
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 C18H15FNG	-	-	NT	NT	NT	NT	NT	NT	NT
 C18H16FN8	+	-	NT	NT	NT	NT	NT	+	NT
 C20H18FN5O	+	-	NT	NT	+	NT	NT	NT	+
 C20H18FN5O	-	-	NT	NT	NT	NT	NT	NT	NT
 C24H26FN7	-	+	NT	+	NT	NT	NT	NT	NT
 C24H26FN8	+	-	NT	NT	+	NT	NT	NT	NT
 C25H27FN8	+	+	NT	NT	NT	NT	NT	NT	NT

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49.

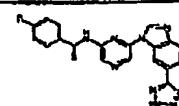
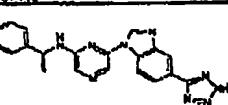
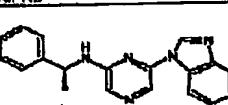
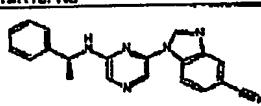
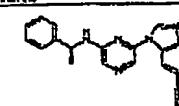
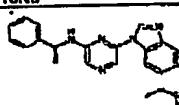
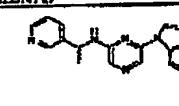
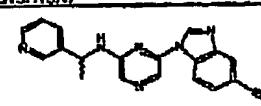
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CHEMISTRY	Jak2	Jak3	zap70	tie2	hck	abl	fms	kdr	btk
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 C24H25FN6	+	-	NT	+	NT	NT	NT	NT	NT
 C26H31FN8	-	-	NT	NT	NT	NT	NT	NT	NT
 C24H27FN6O2	+	-	NT	NT	+	NT	NT	NT	NT
 C21H16N8	+	+	NT	+	NT	NT	NT	NT	NT
 C21H16N6	+	+	NT	+	NT	NT	NT	+	NT
 C24H16N6	-	-	NT	NT	NT	NT	NT	NT	NT
 C24H18N8	-	-	NT	NT	NT	NT	+	NT	NT

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50.

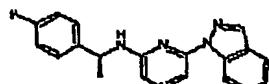
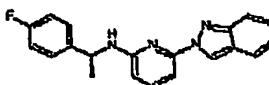
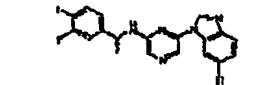
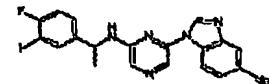
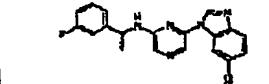
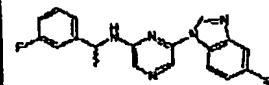
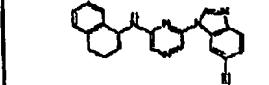
Table 3 (cont.)

CHEMISTRY	Jak2	Jak3	zap70	Er2	hck	abl	tms	ldr	dux
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 C20H16FN9	-	-	+	NT	NT	NT	NT	NT	NT
 C19H16FN5	+	+	+	NT	NT	NT	NT	NT	NT
 C20H16NB	+	+	NT	NT	NT	NT	NT	NT	NT
 C20H16NB	+	+	NT	NT	NT	NT	NT	NT	NT
 C22H25N7O	+	-	NT	NT	NT	NT	+	NT	NT
 C19H16N7	-	-	NT	NT	NT	+	NT	NT	NT
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51.

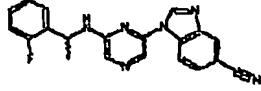
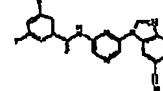
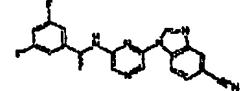
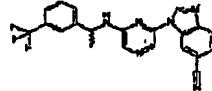
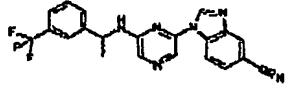
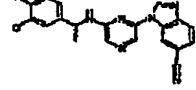
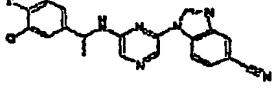
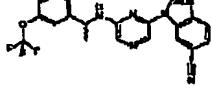
Table 3 (cont.)

CHEMISTRY	JAK2	JAK3	zap70	tie2	nck	abl	fms	kdr	blk
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 C19H16FN5	-	-	NT	NT	NT	NT	NT	NT	NT
 C20H14F2N6	+	+	NT	NT	NT	NT	NT	NT	NT
 C20H14F2N6	+	+	NT	NT	NT	NT	NT	NT	NT
 C20H15FN6	+	+	NT	NT	+	NT	NT	NT	NT
 C20H16FN6	+	+	NT	NT	NT	NT	NT	NT	NT
 C22H16N6	-	-	NT	NT	NT	NT	NT	NT	NT
 C22H16N6	+	+	NT	NT	NT	NT	+	NT	NT

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52.

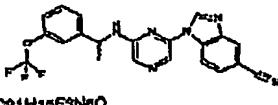
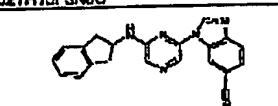
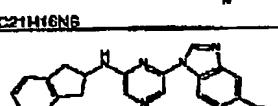
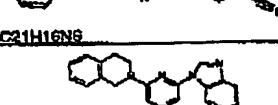
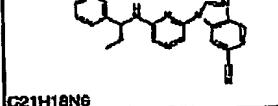
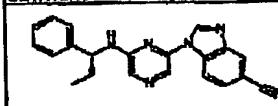
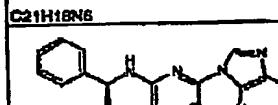
Table 3 (cont.)

CHEMISTRY	Jak2	Jak3	zap70	Src2	hck	abl	fms	kdr	trk
 C20H15FN8	+	+	NT	NT	NT	NT	+	NT	NT
 C20H14F2N6	+	+	NT	NT	+	NT	NT	NT	NT
 C20H14F2N8	+	-	NT	NT	NT	NT	NT	NT	NT
 C21H15F3N8	+	-	NT	NT	NT	NT	NT	NT	NT
 C21H15FN8	-	-	NT	NT	NT	NT	NT	NT	NT
 C20H14ClRN8	+	+	NT	NT	NT	NT	NT	NT	NT
 C20H14ClFN8	+	-	NT	NT	+	NT	NT	NT	NT
 C21H15F3N8O	-	-	NT	NT	NT	NT	NT	NT	NT

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53.

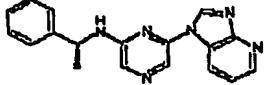
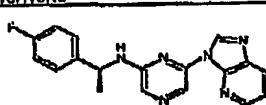
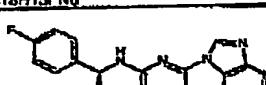
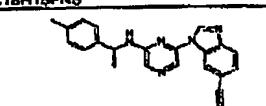
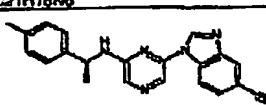
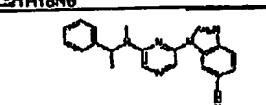
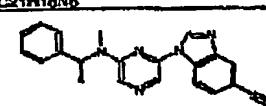
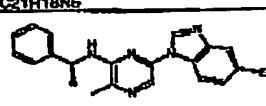
Table 3 (cont.)

CHEMISTRY	JAK2	JAK3	zap70	tie2	hck	abl	fms	kdr	ltk
 C21H15F3N6O	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H16N6	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H16N5	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H16N5	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H16N6	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H16N6	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H16N6	+	+	NT	NT	NT	NT	NT	NT	NT
 C21H16N6	+	+	NT	+	NT	NT	NT	+	NT
 C19H16N6	-	-	NT	NT	NT	NT	NT	NT	NT

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54.

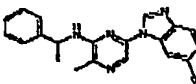
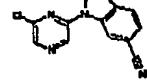
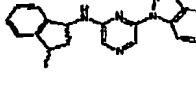
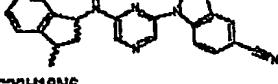
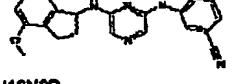
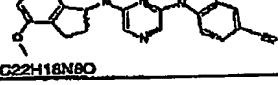
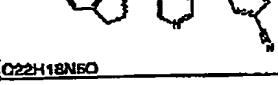
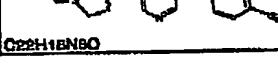
Table 3 (cont.)

CHEMISTRY	Jak2	Jak3	zap70	Uop2	hck	sbl	fms	kdr	dkk
 C16H16N6	-	-	NT	NT	NT	NT	NT	NT	NT
 C16H15FNS	-	-	NT	NT	NT	NT	NT	NT	NT
 C16H15FNS	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H18N6	+	+	+	NT	NT	NT	NT	NT	NT
 C21H18N6	+	-	NT	NT	NT	NT	NT	NT	NT
 C21H18N6	+	+	NT	NT	NT	NT	NT	+	NT
 C21H18N6	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H18N6	+	+	NT	NT	NT	NT	NT	+	NT

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55.

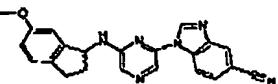
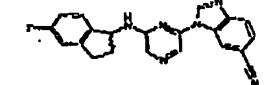
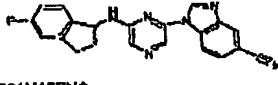
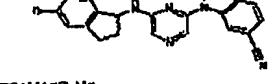
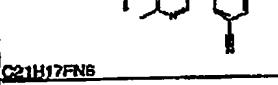
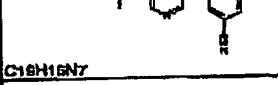
Table 3 (cont.)

CHEMISTRY	Jak2	Jak3	zap70	tie2	hek	apl	fms	kdr	blk
 C21H18N6	+	+	NT	NT	NT	NT	NT	NT	NT
 C12H20N5	-	-	NT	NT	NT	NT	NT	NT	NT
 C22H18N6	-	-	NT	NT	NT	NT	NT	NT	NT
 C22H18N6	+	+	NT	NT	NT	NT	+	NT	NT
 C22H18N6O	-	+	NT	NT	NT	NT	NT	NT	NT
 C22H18N6O	-	-	NT	NT	NT	NT	NT	NT	NT
 C22H18N6O	-	-	NT	NT	+	NT	NT	NT	NT
 C22H18N6O	-	-	NT	NT	NT	NT	NT	NT	NT

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56.

Table 3 (cont.)

CHEMISTRY	Jnk2	Jnk3	zap70	je2	hck	abl	tms	kdr	blk
 C22H18N6O	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H15FN6	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H15FN6	+	+	NT	+	NT	NT	NT	NT	NT
 C21H18BrNa	-	+	NT	NT	NT	NT	NT	NT	NT
 C21H15BrN6	-	-	NT	NT	NT	NT	NT	NT	NT
 C21H17FN6	+	+	NT	+	NT	NT	NT	NT	NT
 C16H16N7	+	+	NT	NT	NT	NT	NT	NT	NT
 C16H16N7	+	-	NT	NT	NT	NT	NT	NT	NT

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57.

It will be appreciated by persons skilled in the art that numerous variations and/or modifications may be made to the invention as shown in the specific embodiments without departing from the spirit or scope of the invention as broadly described. The present embodiments are, therefore, to be considered in all respects as illustrative and not restrictive.

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Dated: 3 December 2003

Cytopia Pty Ltd

10 Patent Attorneys for the Applicant:

BLAKE DAWSON WALDRON PATENT SERVICES

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